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THE EFFECTS OF RADIUM UPON LIVING TISSUES

WITH SPECIAL REFERENCE TO ITS USE IN THE TREATMENT OF MALIGNANT DISEASE

BY

SIDNEY FORSDIKE

M.D., B.S.(Lond.), F.R.C.S.(Eng.)

SURGEON TO OUTPATIENTS, HOSPITAL FOR WOMEN, SOHO SQUARE; GYNÆCOLOGICAL SURGEON TO THE KENSINGTON AND CHELSEA GENERAL HOSPITAL

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PREFACE

As my paper on "The Treatment of Uterine Hæmorrhage by Radium" was a continuation of the investigation of the effects produced by radium upon living tissues, I have included that paper with the Jacksonian Essay.

SIDNEY FORSDIKE.

LONDON,
July, 1923.

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THE EFFECTS OF RADIUM UPON LIVING TISSUES

Historical.

The discovery of X-rays by Professor Röntgen in 1895 led physicists to examine other phosphorescent bodies for the same type of radiation. Becquerel, in particular, studied the phosphorescent substance uranium. He placed a photographic plate, suitably protected, in contact with uranium ore, exposed them to sunlight, and found that the plate had been affected just as though it had been exposed to X-rays. He inferred that the exposure of uranium to sunlight induced the formation of rays akin to the X-ray. He repeated his experiments, but was unable to continue owing to a period of sunless weather, and put the uranium and plates away in a cupboard. Before resuming his experiments he developed some of the plates to ensure that they were good. He was astonished to find that the plates showed shadows as before, and he realised that uranium ore, without the aid of sunshine, was responsible for it. This was the discovery of radio-activity.

Madame Curie took up radio-activity as a subject for a thesis, and found that pitch-blende was even more active than uranium itself, from which she argued that the former must hold some more potent body than the uranium present in it. After prolonged and pains-

taking work she succeeded in separating out a salt of radium, which was two million times more active than uranium itself. She continued her work, but it was only in 1910 that she succeeded in isolating the element radium.

Chemical Properties and Distribution.

Radium is an element of atomic weight 226·45, and belongs to the family group of alkaline earths, which include barium, strontium, calcium, and magnesium. It gives a characteristic bright line in the spectrum and forms salts with the halogens, but differs from its relations inasmuch as it is radio-active. The metal is a pure white substance, which undergoes rapid changes when exposed to the air. It is distributed widely throughout the earth's surface, but occurs in more concentrated forms in uraninite and carnotite.

What is Radio-Activity?

Radio-activity is shown by five effects:

(*a*) Its effect upon a photographic dark plate.

(*b*) Fluorescence is produced in certain substances when brought near to the radio-active body.

(*c*) Ionisation of gases.

(*d*) Production of heat.

(*e*) Effects upon vital tissues.

These effects are produced by the spontaneous atomic transformation of a radio-active substance, in which process rays are emitted. The atomic transformation of radium results in:

(*a*) *Radium emanation*, a gas known to chemists as niton, which gives a distinct line in the spectrum apart from the radium line.

(*b*) An atom of helium with atomic weight 4.

The radium emanation undergoes rapid disintegration, one-half of its potency disappearing in 3·85 days, and in thirty days it has completely decayed. In the process of decay the emanation forms numerous important products, from some of which the therapeutic beta and gamma rays are produced. They are radium A, radium B, radium C, radium D, radium E, radium F, which is known as polonium, and an end product radium G, which is chemically indistinguishable from lead, but having an atomic weight slightly less than that metal. This transformation from radium to an isotrope of lead is interesting, as it appears to solve the ancient problem of the transmutation of metals, and in the radio-active actinium D and thorium D an isotrope of gold would be produced were an A particle given off in place of a B (beta) particle.[1]

Rays Emitted.

There are three different types of rays emitted, Alpha, Beta, and Gamma.

Alpha Rays are material particles with a positive charge of electricity, and are four times the size of the hydrogen atom. They possess considerable ionising power, but are readily absorbed by a layer or two of filter paper or by a thin sheet of metal, and are deliberately excluded clinically owing to their small power of penetration.

Beta Rays are negatively charged electrons and are soft, medium, and hard according to their power of penetration. The soft rays approach the alpha ray in penetrating power, while the hard rays have a penetrating power a hundred times that of the alpha ray. Rutherford estimates that hard beta rays may be absorbed to the extent of one-half by 0·1 mm. and com-

pletely absorbed by 2·0 mm. lead, and to the extent of 94 per cent. by 1 cm. of epithelial tissues.

Gamma Rays are electro-magnetic waves, similar to X-rays, but the wave length is from 20-30 times shorter than the latter. The hard gamma ray is only half absorbed by 14 mm. lead, and according to Rutherford 26·5 cm. of soft tissue would be required for their half absorption. According to the investigations of Giraud, gamma rays are reduced to one-half after passing through 7·6 cm. of muscle tissue.

Secondary Radiation.

All three types of ray produce secondary radiations when they impinge upon matter, and the power and intensity of this radiation increases greatly with the atomic weight of the matter impinged upon. These secondary radiations are screened off by the employment of gauze, filter paper, or rubber tube.

Filtration of Rays.

The principle of filtration was introduced by Wickham, Degrais, and Dominici, with the object of absorbing the less penetrating rays, and so preventing injury to the superficial structures, while the deeper tissues were being adequately exposed to the hard rays. Filtration is carried out by means of screens of varied thickness and of different metals, such as lead, silver, platinum, etc.

Effects of Radium upon Living Cells.

(*a*) Bacteria.—Chambers and Russ[2] prepared emulsions of various organisms—*Bacillus prodigiosus*, *streptococcus*, *staphylococcus*, etc.—and exposed them to the influence of radium rays, and found that the emulsions

were sterilised, the time necessary being proportionate to the dose of rays given. No experimental results have been obtained *in vivo* to suggest that bacteria can be destroyed without at the same time producing grave injury to the normal tissues.

(*b*) Lower Forms of Animal Life.—Halberstaedter[3] radiated trypanosomes and observed the result upon their motility and power of infecting animals. With the doses employed the motility was apparently unaffected, but the power of reproduction, and consequently of infection, was checked. He inferred that the radiation destroyed the reproductive function of the organism before the nutritive function was injured. Numerous other observations upon ova and spermatozoa have been recorded, the former developing more slowly and erratically, the motility of the latter being affected the most.

Effects upon Tissues of Higher Animals.

Skin.—The reaction appears usually from the seventh to the tenth day, but with an excessive dose may appear earlier. Four degrees may be recognised: (1) Simple erythema; (2) erythema followed by desquamation; (3) vesication with superficial ulceration; (4) deep ulceration. Delayed reaction of 4-6 weeks sometimes occurs, and a secondary reaction may take place many months after the exposure. The resulting scars are white and supple and may remain peculiarly responsive to changes of temperature for some months. Histologically the main feature is a development of connective tissue, characterised by the uniformity of the superimposed connective tissue fibres lying parallel to the surface.

When ulceration is produced, it is intractable and

may take months to heal. Telangiectases are apt to ensue as a late effect, and in cavities like the vagina a steadily increasing fibrosis follows upon several exposures.

Blood.—Observations by Mottram[4] upon the blood of workers with radium, and experimental results from the injection of emanation solution into the circulation show the important effects are at first to produce:

(*a*) An increase in the red cells which lasts but a short time.

(*b*) A transient leucocytosis, soon followed by a pronounced leucopenia. Prolonged exposures result in destruction of the white cells and hæmolysis of the red cells, the leucopenia falling largely upon the polymorphs and the lymphocytes. This blood reaction is of great importance clinically, as the blood index constitutes a criterion by which to judge the advisability of exposure to radium.

Spleen and Lymphatic System.—Radium rays exert a decided effect upon these organs, increasing the connective tissue, diminishing the cellular tissue, and completely destroying the lymphocytes. In the bone marrow there is an accumulation of red cells, with scattered hæmorrhages throughout its substance.

Blood-Vessels.—The endothelium is extremely sensitive to radiation, the cells swelling up and proliferating, and finally obliterating the lumen.

Connective Tissues, Muscle, Cartilage.—White fibrous tissues appear to undergo destruction, a direct contrast to the effect upon yellow elastic fibres, which are peculiarly resistant, and show no change even after prolonged exposure.

Muscle fibres are replaced by connective tissue fibres.

Cartilage is initially destroyed, but hypertrophic changes may be noted in it.

Nervous System.—Horsley and Finzi[5] from experiments upon the brain of monkey concluded that the central nerve tissue was relatively insensitive, and considered that the changes noted were due to the circulatory disturbance produced.

Peripheral Nerves. — Horowitz found atrophic changes in the axis cylinders, with destruction of the myelin sheath of sciatic nerves irradiated.

Changes noted in the Ovary.—A series of experiments were undertaken to ascertain the changes induced in a tissue when radium was placed in contact with it. Changes have been described by the irradiation of an organ through the skin, but such conditions were, in the main, foreign to the conditions which obtain in the treatment of malignant disease in the human being, and the distance between the organ and the source of irradiation possibly meant many fallacies. Furthermore, in intimate exposures of growths to radium there is always the factor of infection to be considered, and one which may lead to grave consequences.

The ovary was chosen as a suitable organ because it is situated away from the surface, the cells are rapidly growing and therefore radio-sensitive, and, finally, two or three observations have been published upon effects produced through the body wall. The tissues of a cat are so much finer than those in man, that the length of exposure was a matter of difficulty at the outset, for while anxious to obtain standard results of a series of experiments, it was important to see the early changes.

Exposures.—½ hour, 1 hour, 2, 3, 4, 5, 6, 7 hours were given at first, and later 10½, 12½, 15, 19, and 24 hours, the last two sufficing to destroy the ovary beyond recognition under the microscope. The animal was allowed to survive the exposure for varying periods of time from thirty-six hours to twelve weeks, and, finally, a prolonged series of seven-hour exposures were studied, this being the optimum time for noting effects.

Technique.—The implantation of the radium was carried out on the ordinary surgical principles of asepsis. The animal was anæsthetised with ether, the abdomen shaved and cleansed in the usual way. The abdomen was opened in the mid-line and the ovary exposed. A tube of radium sulphate, contain- 50 or 100 mgrms., screened with 0·5 mm. silver and 1 mm. brass, covered with a rubber tube 3 mm. thick, was fixed to the posterior wall of the abdomen in the neighbourhood of the kidney. A suture was then passed through an avascular part of the mesovarium and then through or around the rubber tube, bringing the ovary into contact with the radium. It is important to avoid interfering with the blood supply of the ovary, otherwise the effect would be in part due to the radium, and in part due to the modified vascular supply of the organ. The abdomen was closed, and seven hours later opened again under anæsthesia for removal of the radium. In the early experiments an attempt was made to see the effects upon other organs at the same time, but that can only be done with certainty by fixing a definite portion of an organ to the radium, and this was found to embarrass the animal, so it was abandoned.

The immediate macroscopic effect was the exudation of a small quantity of peritoneal fluid and a fairly

extensive engorgement of the tissues in the neighbourhood of the radium. These effects had disappeared by the time the animal was killed, but in one animal proceeded to suppuration, which necessitated its destruction.

Post Mortem.—The great omentum was usually lightly adherent to the scar, otherwise the abdomen appeared normal; but the irradiated ovary and the upper end of the Fallopian tube were strongly adherent, and frequently the ovary had to be dissected away from the tube with a knife. In the very long exposures, nineteen and twenty-four hours, the ovary was shrunken to such an extent and the two tissues were so united that the two were removed in one piece, and sections taken through both organs at once. The irradiated ovary was very much smaller than the opposite ovary, sometimes being reduced to as much as one-half or even one-third in size. The adhesions were consequent upon an aseptic inflammation, for in none of the cases was there any sign of a round-celled infiltration, and the formation of fibrous tissue was limited to the area of contact with the radium. In a later series of cases the ovary was exposed to 100 mgrms. of radium sulphate, but in these cases the radium tubes were placed within a puerperal Fallopian tube, and the ovary was lightly anchored to the wall of the Fallopian tube.

The results will be considered under the following heads:

(*a*) The effects in general.

(*b*) The varying dose, with duration of life from ten to twenty-one days.

(*c*) Seven-hour dose, with duration of life 36 hours, 60 hours, 5 days, 7, 13, 21, 42, and 84 days.

(*a*) *General Effects.*—It soon appeared that there is a minimum dose (dose = length of exposure + quantity of radium employed), below which no structural change can be noted. It also appeared that with maximum exposures there was such complete destruction of the tissue that microscopically it could not be identified. The changes observed are gradual and progressive, and the whole tissue is not affected to the same extent at the one time. There is a marked difference in reaction time of the various tissues — *e.g.*, while the large Graafian follicles are completely destroyed, the primary follicles show no characteristic variation. The primary follicles, and still more the stroma and vessels, require a much larger dose of radium before gross changes are shown. In many sections exposed beyond the limit for destruction of the large Graafian follicles, but where the primary follicles are only partially destroyed, numerous large corpora lutea are seen filling the section. These luteal bodies could not have been derived from the original mature follicles, for they were destroyed, but they were probably formed from some of the primary follicles, which had not been affected injuriously, but in which the radiation had produced a hastening of maturation. It would also seem that once a follicle is influenced sufficiently to show microscopic change, there is no subsequent recovery. The most constant early change is the disappearance of the ovum from the large follicle; the contents remaining are without form or structure. In the small follicles a similar change is observed, but many retain the ovum, which, however, stains so lightly that more minute structure cannot be determined; in practically all, even where the ovum re-

mains, the granulosa cells show shrinkage and vacuolation, and the primary follicles are finally noted as irregular spaces in the cortex.

(*b*) *Varying Dosage with Varying Duration of Life.*—Small exposures of thirty and sixty minutes produced no gross structural change in any of the ovarian tissues. With two hours' exposure the large Graafian follicles are completely destroyed, and appear as large irregular spaces filled with a poorly staining, structureless mass without cells or cell outlines, and even the membrana granulosa cells cannot be made out, whereas the primary follicles show no characteristic change at this time. At three hours' exposure it cannot be said that any definite change has taken place in the primary follicles, but at four hours very marked changes are noted—viz., ova have disappeared from many, and of the remaining some stain badly and the nucleolus cannot be made out, whereas there are some which do not appear to have been influenced at all. From four hours on, the primary follicles become more and more affected, until at the higher exposures they are also completely destroyed. No constant change is noted in the endothelium of the vessels before an exposure of seven hours is given; at that time the cell outlines of the endothelium are lost in many sections, and the nuclei, instead of being arranged circumferentially, are seen to be lying at right angles to the vessel wall, as though the cells had been broken up and twisted towards the lumen; this appearance becomes more pronounced with the higher exposures, and finally numerous small vessels are to be seen entirely obliterated. The cells of the stroma remain resistant until a much higher exposure is given; then they are observed to be comparatively few and very lightly stained.

(*c*) *Seven Hours' Exposure* with increasing duration of life.

Duration of Life Thirty-six Hours.—Engorgement of vessels with diffuse hæmorrhages into the stroma.

Sixty Hours.—Similar appearance with hæmorrhage into some of the large Graafian follicles, while others are destroyed, and some are practically normal.

Five Days.—Large follicles destroyed. Small follicles showing pronounced changes—viz., loss of ovum, vacuolation, with cellular débris.

Seven Days.—Most of the small follicles are represented by irregular empty spaces; a few retain a degenerate ovum, and some show cellular outlines. The endothelium of the vessels is now showing change, the cell-wall being lost and the nuclei turned at right angles to the lumen.

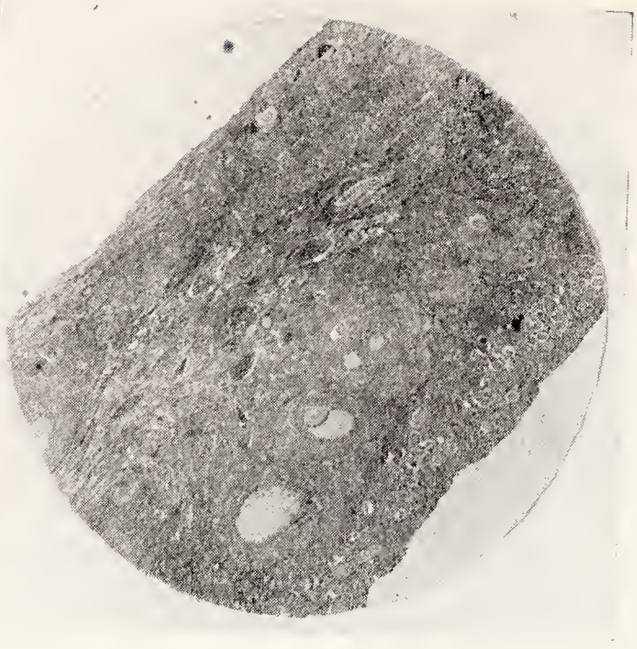
Thirteen Days.—Small follicles distorted, mostly empty, some with ova, and some with remains of cells. The change in the endothelium of the smaller vessels is more pronounced. Stroma largely filled by corpora lutea.

Twenty-one Days.—Some faintly staining ova are still apparent, the follicle-wall being a basement membrane with no cells. Many small vessels occluded, and the middle coats are thickened.

Forty-two Days.—Small follicles are present, irregular in shape, with poorly staining ova, and some cellular structure remains. The stroma is scanty, owing to the presence of large corpora lutea.

Eighty-four Days.—Small follicles are few, irregular, and distorted; no recognisable ova are present. Corpora lutea present; stroma scanty.

In nineteen and twenty-four hours' exposure the ovarian tissue is hardly recognisable, and there is more



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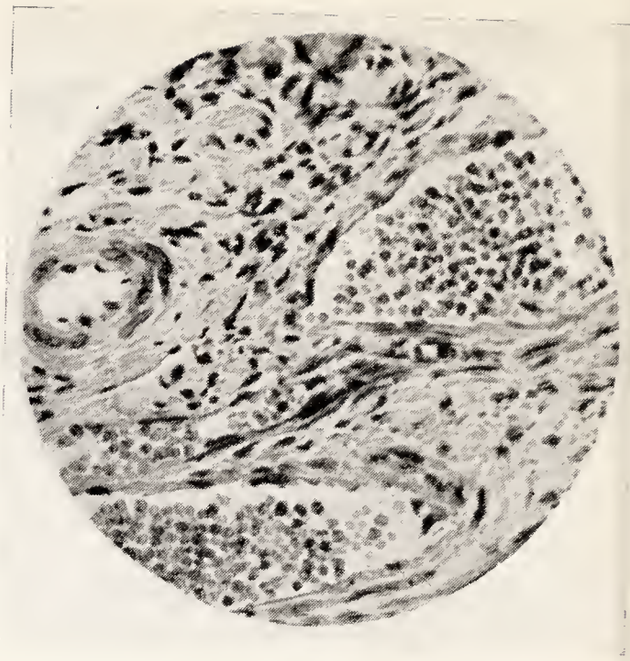

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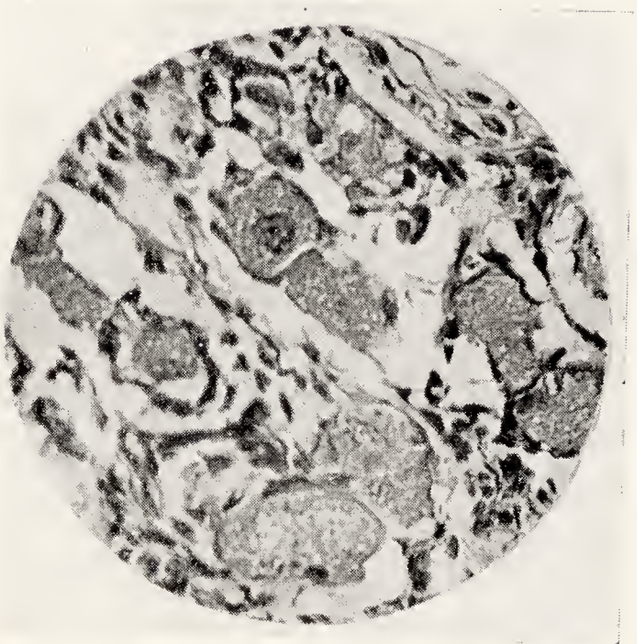

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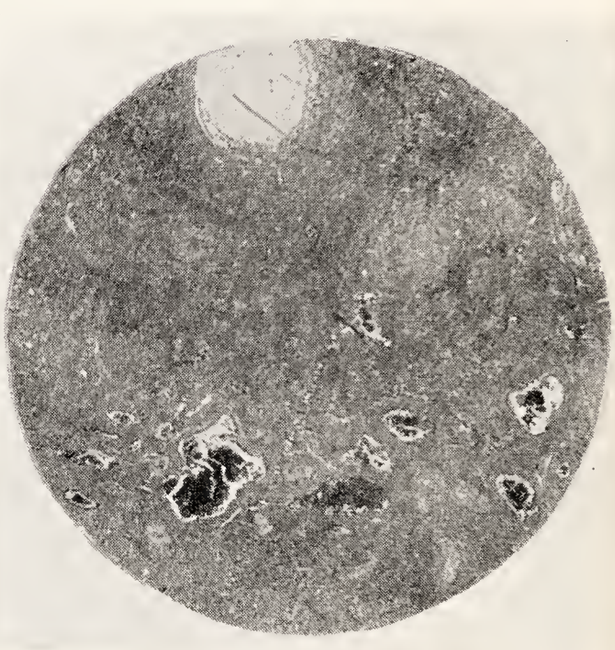

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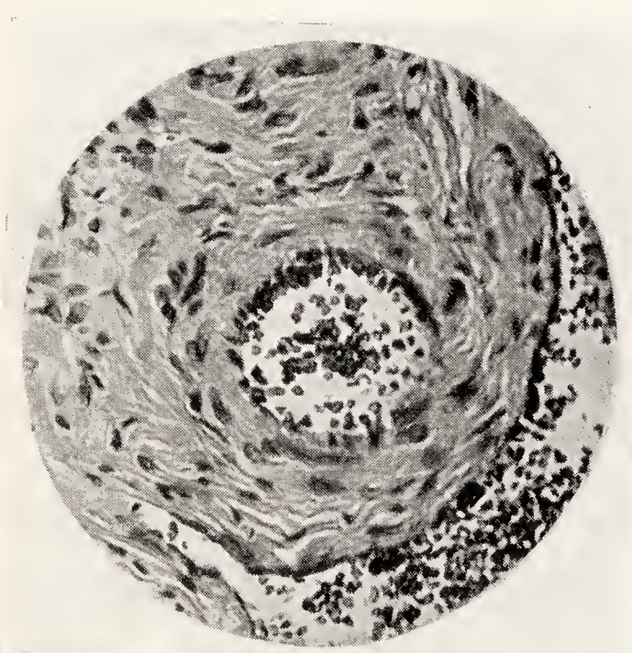

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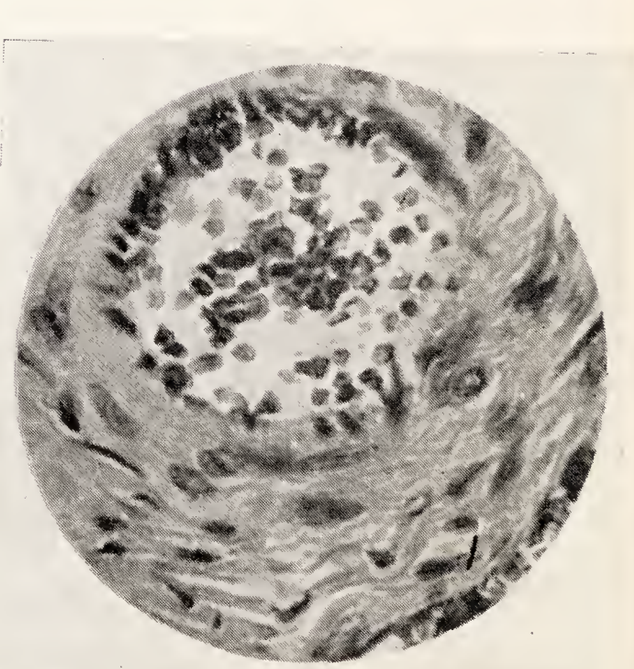

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tubal than ovarian tissue in the field. There is nothing left of follicles of any kind; a few scattered stroma cells remain, but the major part of the section is made up of fibrous tissue.

Exposure for Seven Hours (Animal survived Thirty-six Hours).

No. 1. *Low Power.*—The large and small follicles show little change. The stroma shows engorgement of vessels and diffuse hæmorrhages.

No. 2. *High Power, Same Section.*—Vascular engorgement and hæmorrhage into the stroma.

No. 3. *High Power, Same Section.*—Small follicles are practically unaffected.

Exposure Seven Hours (Animal survived Sixty Hours).

No. 4. *Low Power.*—Shows vascular engorgement and two large follicles, one of which is filled with structureless débris.

Nos. 5 *and* 6. *High Power.*—The endothelium of the vessels shows changes in parts of the section, the nuclei being deeply stained and at right angles to the lumen of the vessel; no cell-wall can be seen. In No. 6 it is still better shown, where the endothelium is entirely destroyed on one side of the vessel, and forms a contrast with the opposite side.

No. 7. *High Power, Same Section.*—The small follicles are beginning to show changes—vacuolation, shrinkage, and irregularity. Many, however, contain an ovum and nucleus, which appear normal in every respect.

Exposure Seven Hours (Animal survived Five Days).

Large follicles have disappeared, and several corpora lutea are present.

No. 8. *High Power.*—Many of the small follicles are vacuolated, but show a few cellular outlines; but many show faintly staining ova, which do not come out in the photograph.

No. 9. *High Power, Same Section.*—Shows the change in the endothelium of the small vessels.

Exposure Seven Hours (*Animal survived Seven Days*).

No. 10. *High Power.*—Small follicles highly vacuolated, and show some cell remains. Some show faintly staining ova, but no germinal spot can be detected.

No. 11. *Another Part of Same Section.* — Shows shrinkage of the follicular contents, but the destruction is not so advanced as the last photograph.

No. 12. *High Power.* — Destruction of endothelium of vessels is more advanced.

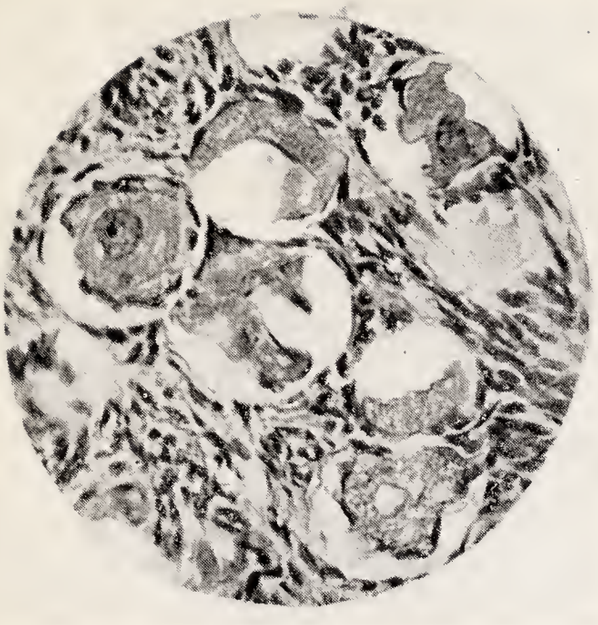
Exposure Seven Hours (*Animal survived Thirteen Days*).

No. 13. *Low Power.* — Shows the stroma almost entirely occupied by corpora lutea, and two irregular spaces which represent large Graafian follicles. The small follicles are seen as minute spaces some distance below the surface of the ovary.

No. 14. *Small Follicles of Same Section under the High Power.*—Some contain an ovum, with several deeply staining fragments replacing the nucleolus, which is surrounded by the follicular contents broken away from the follicular wall. Many are irregular empty spaces.

Exposure Seven Hours (*Animal survived Twenty-one Days*).

This is an instructive section, for through some failure in technique the ovary was not irradiated to the



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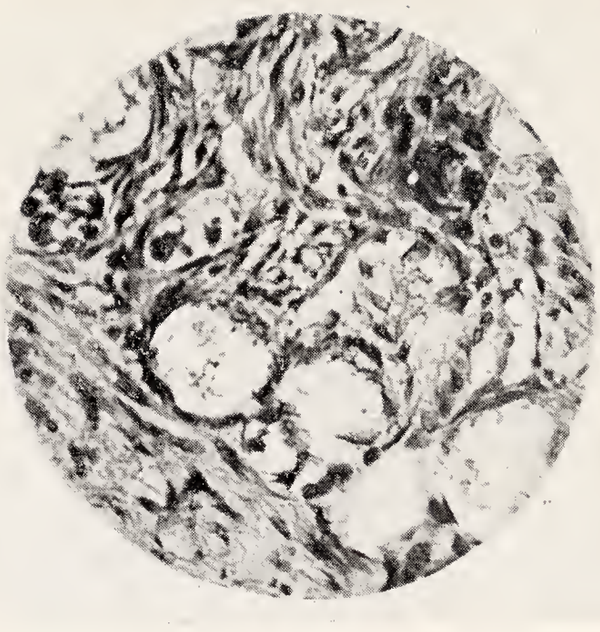

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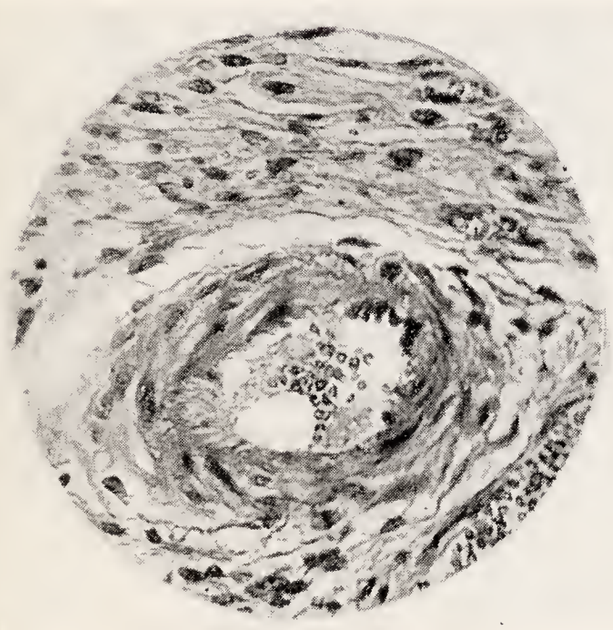

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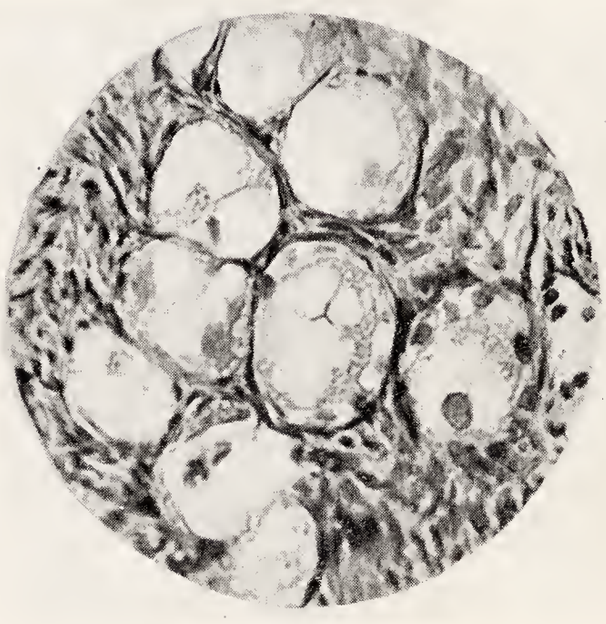

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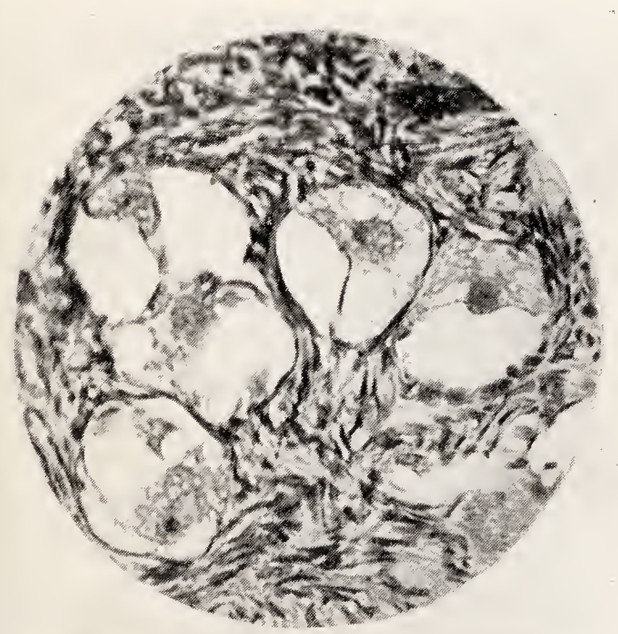

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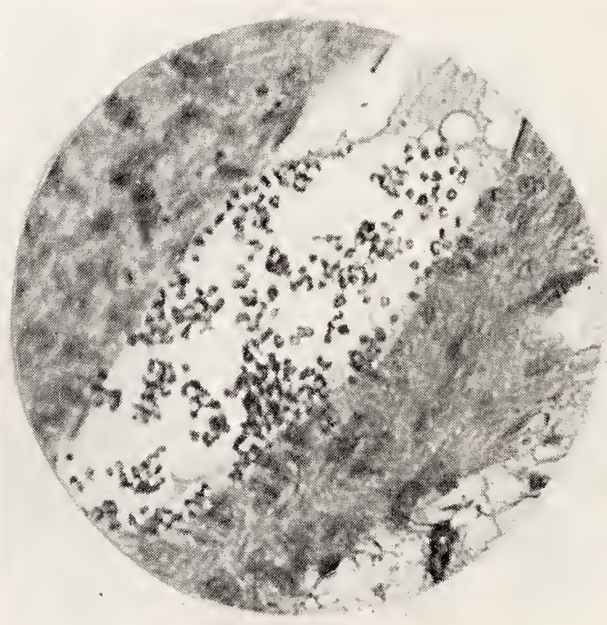

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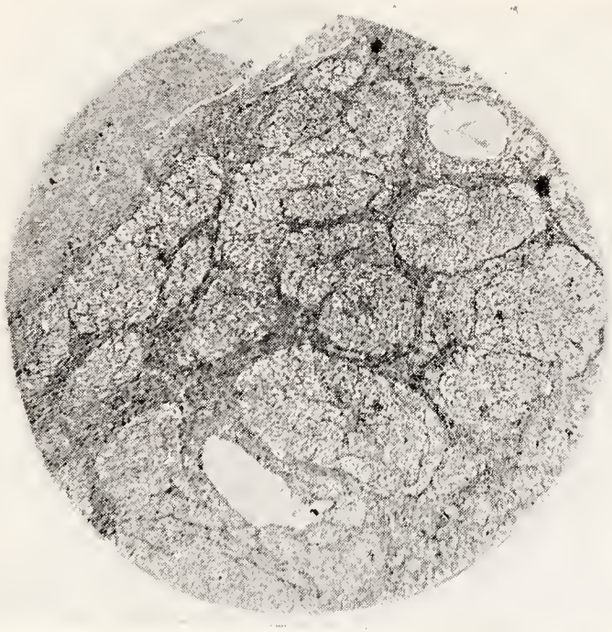

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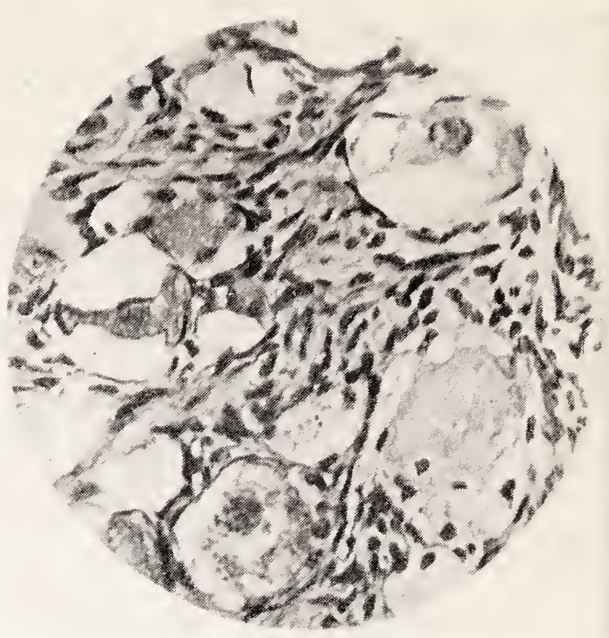

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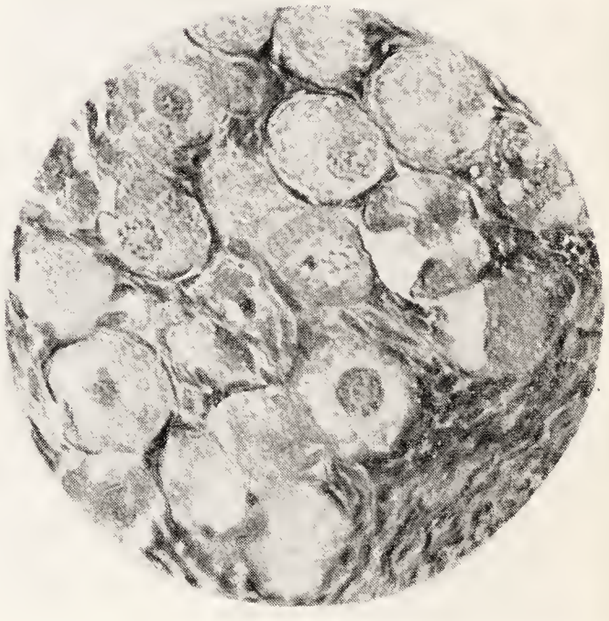

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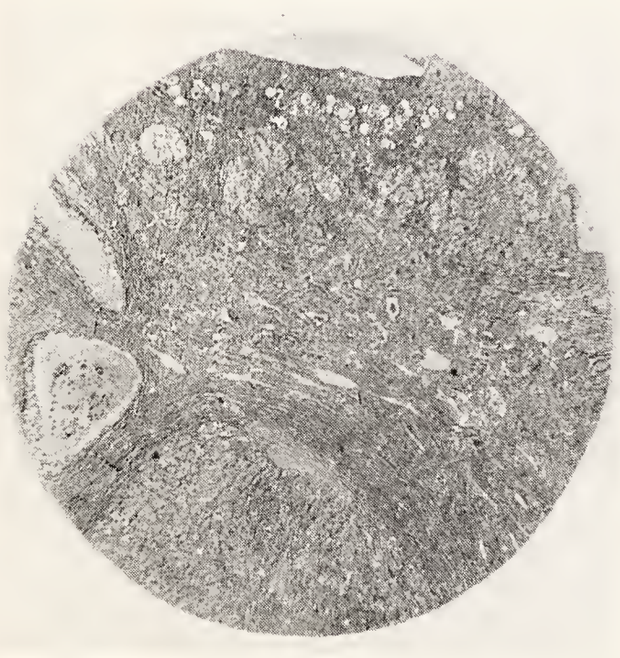

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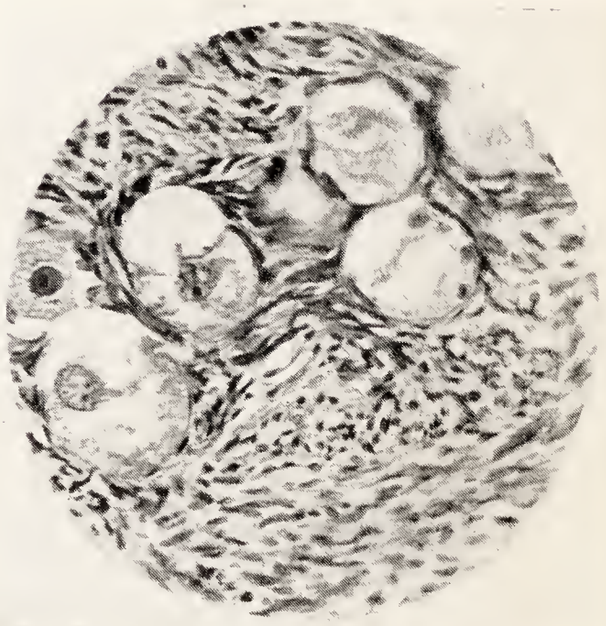

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same extent as in the other experiments, and early effects upon the ova were obtained.

No. 15. *Low Power.*—The normal and the irradiated ovary are nearly equal in size. The number of small follicles is very striking, but quite normal, for the ovary of the other side which was excised at the time of the implantation of the radium shows a similar large number. The vessels are dilated, but no change is shown in the endothelium. A few normal corpora lutea are found, and some large Graafian follicles just beyond maturity.

No. 16. *High Power of above Section.*—A bunch of small follicles which are almost normal in appearance. They are regular in shape, the cells of the follicular wall and their nuclei are visible. The cellular contents of the follicle are well shown, with an ovum in the middle of it. In some the ovum has disappeared and the cells are losing their outline, with vacuoles appearing amongst them. The ovum is well shown in many of the follicles, but a single nucleolus is replaced by numerous deeply staining fragments scattered throughout the ovum, the broken-up chromatin elements. These nuclear changes are believed to be the earliest effects of irradiation upon the cell, the changes in the cytoplasm being secondary. They are occasionally shown in the earlier sections.

Exposure Seven Hours (Animal survived Forty-two Days).

No. 17. *Low Power.*—A striking contrast in the number of small follicles when compared with No. 16. It shows some large follicles undergoing compression and retrogression, and a number of corpora lutea.

No. 18. *High Power.*—The small follicles are largely

destroyed, some retain their shape and a few cell remnants, some contain ova which show different stages of degeneration, and one even looks more or less normal.

Exposure Seven Hours (*Animal survived Twelve Weeks*).

No. 19. *Low Power.*—The whole field is occupied by corpora lutea, and in the region of the cortex a few irregular spaces can be seen which represent small follicles.

No. 20. *High Power.*—A few irregular spaces indicate the remains of the small follicles. The stroma cells are fewer and less characteristic, many of the small vessels are occluded.

Exposure Nineteen Hours (*Animal survived Twenty-one Days*).

No. 21. *Low Power.*—The ovary has shrunken to a structure one-third of an inch in length, but retains its oval shape and is in complete tissue continuity with the upper end of the tube. The section was taken through both organs, and parts of the Fallopian tube can be recognised; some large vessels are present and a considerable amount of fibrous tissue. No ovarian tissue can be identified.

No. 22. *High Power.*—A few stroma cells are seen, but nothing characteristic of ovarian tissue.

Twenty-four Hours' Exposure reduces the ovary to a similar condition, where no character is left in the tissue.

Half-hour and One Hour Exposure, with twenty-one days' survival, shows no change beyond capillary engorgement.

General Conclusions.—With strong doses of radia-

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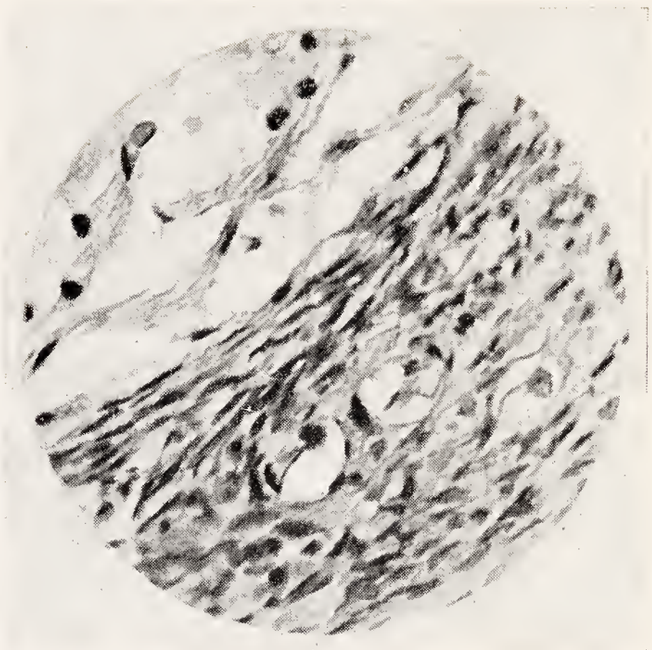

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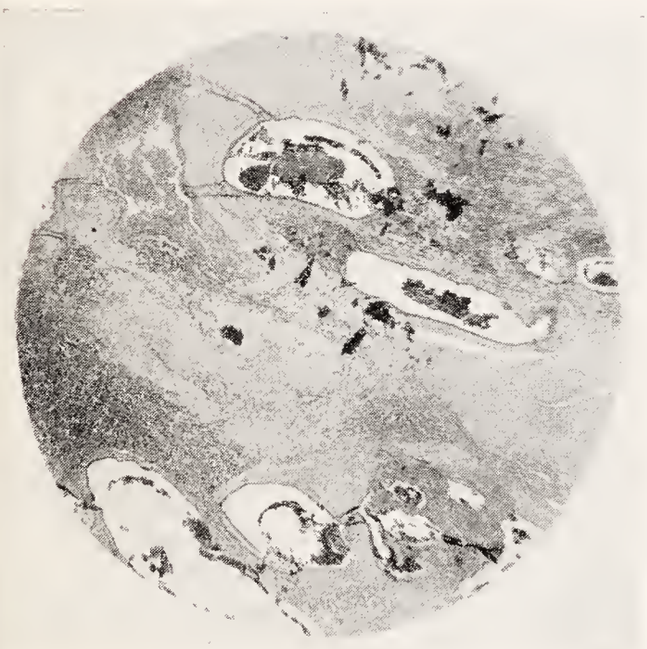

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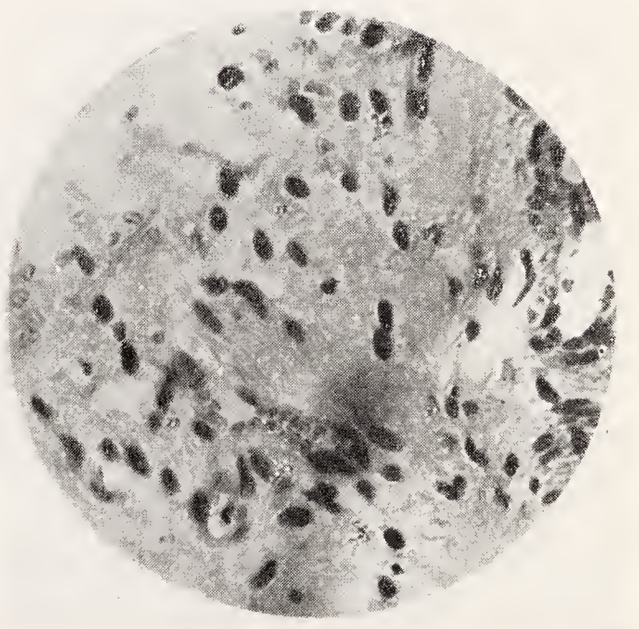

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tion where the radium is brought into direct contact with the tissue, the effects are procured in a few hours. With moderate doses there is a definite latent period before any change is noted, but the microscopical changes are identical though delayed.

That apart from the engorgement of vessels and hæmorrhages, the first noticeable effect is upon the nucleus of the primary follicles, where one of the above noted changes takes place, and the cytoplasm of the cell only shows changes later, and therefore the cell is probably killed by action upon the nucleus.

That radium rays show a differential action upon vital cells—*e.g.*, endothelium of vessels, ovarian follicles, lymphatic tissues and white blood cells are rapidly destroyed, whereas nervous, fibrous and cartilaginous cells are more resistant. This differential action is shown more markedly in rapidly dividing and embryonic tissues, and it is upon this selective action that the clinical treatment of tumours is founded. The ultimate action upon the nucleus and cell life remains a secret, and until the chemistry of the cell is cleared up will probably continue so.

Effects of the Different Rays.

Alpha Rays may be utilised alone by employing polonium, and are said to produce an inflammatory reaction in the skin. According to Beckton and Russ,[6] the disappearance of Altmann's granules from cells of healthy tissues is attributable to the action of alpha rays. Clinically the alpha rays are all absorbed by the radium container and are therefore excluded.

Beta Rays.—In the employment of these rays unscreened radium is used, but to use them without the gamma ray presents considerable difficulties.

Abbé deflected the beta rays by means of a strong magnet, and thus used them without the gamma ray. He achieved some success in the treatment of certain skin diseases; but in ordinary practice the utilisation of the beta rays is never employed without gamma rays.

Gamma Rays can be used alone by the use of a screen of 2·0 mm. lead. Colwell and Russ came to the conclusion that "different rays give rise to quite different effects upon one and the same variety of cell." Gudzent and Levy,[7] after numerous experiments and exhaustive work upon various tissues, furnish convincing evidence that the histological effects of the alpha, beta, and gamma rays are identical.

Effects of Radium upon Malignant Cells.

The effects of radium upon the rat and mouse tumour have been noted by Bashford, Murray, Chambers, Russ, Wood, Wedd, Wassermann, and numerous other workers, and some of the experiments must be mentioned. Wedd, Russ, and Chambers[8] showed that excised portions of mouse tumour, exposed *in vitro* to radium, could no longer be successfully inoculated into a new host. Smaller doses checked, but did not inhibit, the growth of the inoculated tumour. They concluded that the changes set up in the tumour by the irradiation were responsible for the variability and inhibition of the growth. Von Wassermann carried out similar experiments, and came to the conclusion that the power of propagation of the cells was primarily affected, and, secondarily, the nutritive function of the cell. Wood and Prime[9] carried out a series of experiments with various animal carcinomata, tumour cells being exposed to irradiation both *in vivo* and *in vitro*.

In one series of experiments the tumour tissue was exposed *in vitro* to beta and gamma rays, and it required only ten minutes' exposure to 83 mgrms. radium, and twenty minutes' exposure to 17 mgrms. to kill the tumour cells, as evidenced by subsequent inoculation.

In a second series of experiments *in vitro* the tumour cells were exposed to hard beta and gamma rays, and 83 mgrms. radium killed the tumour cells in sixty minutes, 17 mgrms. requiring three hours to produce the same effect.

In a third series of experiments pure gamma rays were employed, and they found that 83 mgrms. took seven hours to destroy the tumour cells, and 17 mgrms. took twenty hours.

In another series of experiments hard beta and gamma rays were used over a tumour in the tissues of the animal. Exposures of not more than two hours were given, which somewhat vitiates the results. The experimenters observed that upon subsequent inoculation into other animals some slowing of growth took place, as compared with controls, but the irradiated cells were not killed. Further, they noted that tumour cells, more than 1·1 cm. away from the radium tube, grew as well and perhaps better than the controls when inoculated into other animals. As the beta rays are absorbed by 1 cm. of tissue, this experiment apparently shows that gamma rays could not destroy cells *in vivo* in two hours, although *in vitro* it succeeded in one hour. They drew the following conclusions from their experiments :

(*a*) Hard beta rays plus gamma rays have eight times the lethal power of the pure gamma rays, but as

beta rays are so easily absorbed (1 cm. tissue), gamma rays are necessary for deep results.

(*b*) Sublethal exposures slow the growth of tumour cells for a certain length of time, while still shorter treatments seem to stimulate the cellular activities.

(*c*) The dose of rays required to destroy tumour cells *in vivo* is greater than that necessary to destroy isolated cellular elements.

Effects upon Human Carcinoma.

The observations upon human carcinoma cells are necessarily limited, for it is obviously undesirable to remove pieces of tissue at frequent intervals from a cancer. The notes recorded below are based upon the appearance of the growth before radium is used, and again from ten to thirty days later, when the tumour is being irradiated for the second or third time. In ten days the symptoms have materially abated as regards hæmorrhage, pain, and discharge, and in appearance the ulcerous cavity is much reduced in size, clean, and looks like a healthy healing ulcer, with epithelium growing in to cover the new tissue formed; the walls are firm, and neither break down nor bleed save for a little oozing if the epithelium be rubbed off. In the section cut before irradiation, the microscopical field is entirely occupied by solid masses of malignant cells. In the section prepared from the tenth to twentieth day, the masses of cells are broken up into islets, surrounded by young connective tissue; diffuse hæmorrhages are seen scattered through the section, with round-celled infiltration. The individual malignant cell is rather larger, but irregular, and stains indifferently, and in some of the sections fusion giant cells are seen. The nuclei appear to contain

numerous irregular masses, which stain darkly, and which represent the broken-up chromatin elements.

At a later period the malignant cells are reduced in number, many of them have lost their nuclei and cytoplasm, and show up as empty spaces surrounded by a cell-wall. Some retain both nuclei and cytoplasm, but stain so lightly that they would pass for mirror-images of real cells; in this condition, although they are undoubtedly malignant cells under the microscope, in a negative the shadows are too indistinct for diagnosis. The islets of cells are surrounded with fibrous tissue, and present the appearance of being strangled in the grip of this tissue.

At a later period the cells become fewer and fewer, and only occasional mirror-images are seen in the grip of the fibrous tissue. Later sections may fail to show a single malignant cell, but a striking accession of fibrous tissue, and at this time the ulcer has healed and presents a smooth scar.

In virulently infected cases, if exposed to radium without pre-radiation treatment, a massive necrosis may take place, and microscopic examination reveals no favourable alteration in the growth.

In scirrhous growths, with the formation of a large quantity of fibrous tissue, malignant cells may be recognised in the section from two to three months later, but the staining reaction is low.

A. *Low Power* shows, very inadequately, solid masses of malignant cells, which have invaded the muscle tissue of the cervix in a late stage of the disease, and before exposure to radium.

B. *Low Power.*—A piece of tissue removed seven days later shows scattered islets of malignant cells surrounded by young fibrous tissue.

C. *High Power* of the same section shows the carcinoma cells, containing numerous black dots—the broken-up chromatin elements. Some of the cells show vacuoles, some are mere cell outlines, while others have stained too lightly to show up in the negative.

D. *Low Power.* — Section taken twenty-one days from initial exposure. A few malignant cells are seen in and bordering a tear in the section; these cells are variable in size and staining reaction. The nuclei are irregular in shape in some of the cells; in others the nucleus has disappeared, and the chromatin is broken up into numerous fragments. In yet others a faint indication of a nucleus remains in a cytoplasm which stains lightly. All stages of vacuolation can be seen, until finally the cell is represented by a space surrounded by a basement membrane. The stroma consists of young connective tissues, plasma cells, and some polymorphonuclear cells, with minute hæmorrhages. Occasionally a mirror-image of a malignant cell may be seen, but it is too faint to present any structure or to appear in the negative. In parts of the section scar tissue is present.

E. *High Power, Same Section.*—Shows the stroma, with a few scattered carcinomatous cells entangled in fibrous tissue; they are not distinctive, the cytoplasm being vacuolated and consequently staining badly.

F. *High Power.*—Sections of cervix showing squamous carcinoma before exposure to radium.

G. *Same Section with Higher Eye-piece.*—Definition of cells is lost.

H. *Section from the Same Cervix* two months later after three exposures to radium. The section is largely composed of dense scar tissue. A few carcinomatous

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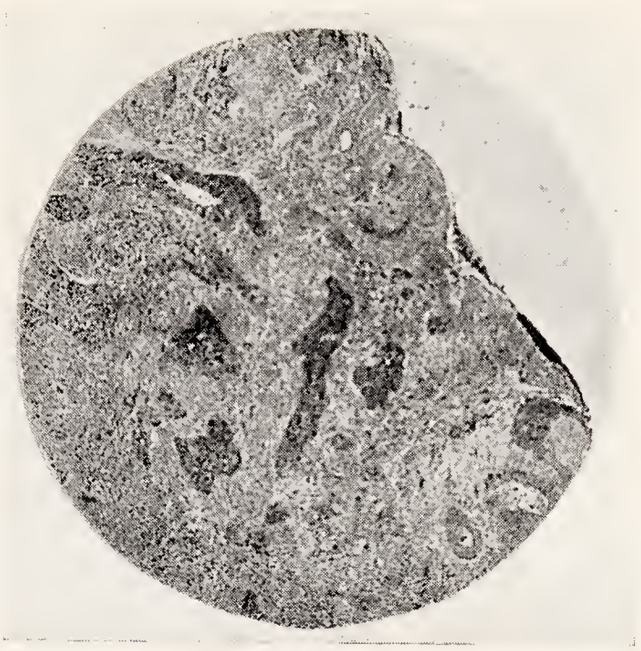

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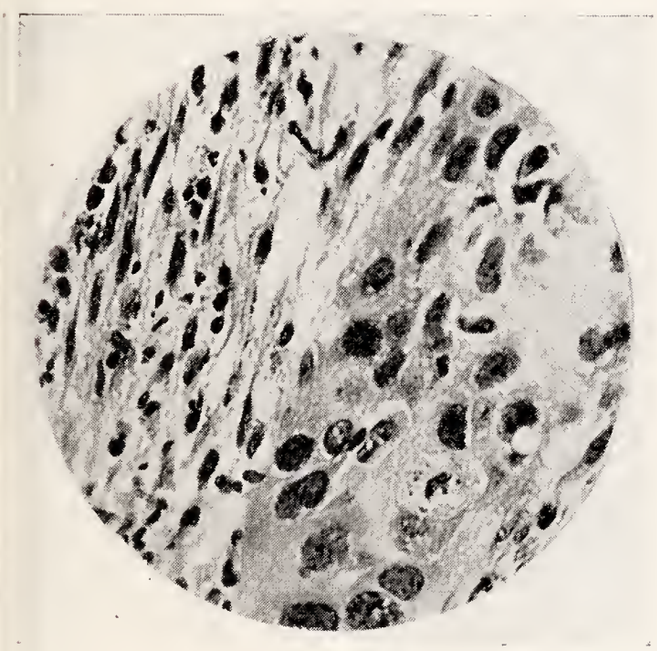

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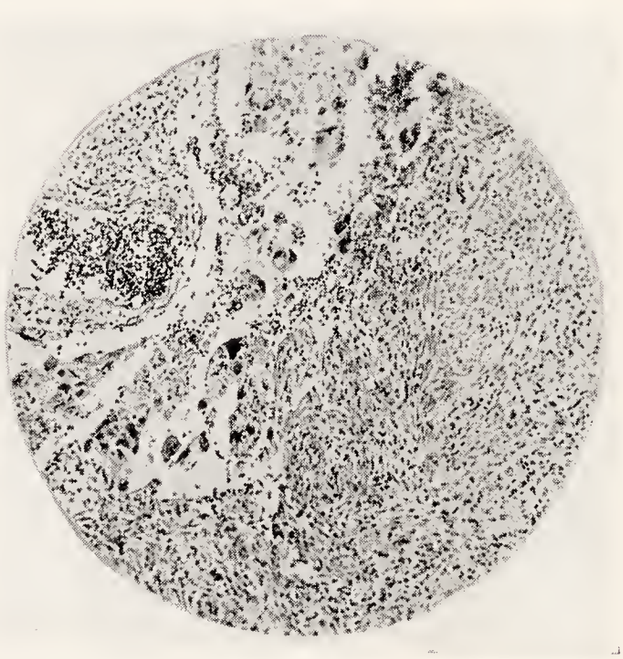

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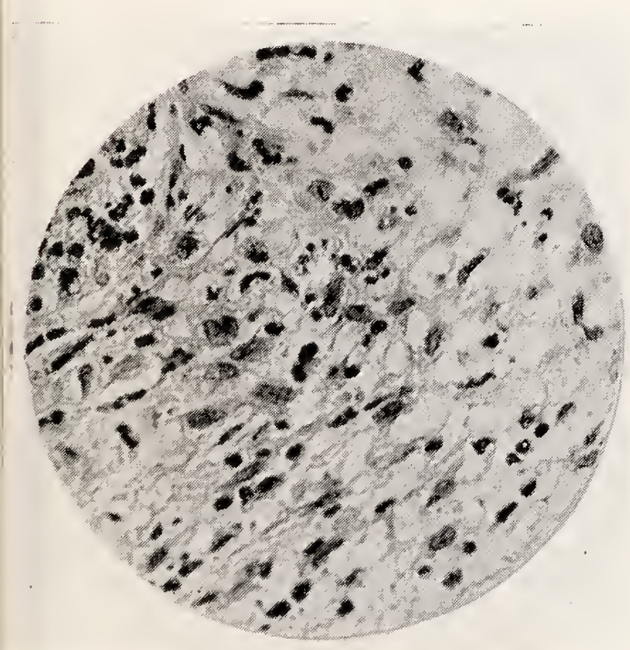

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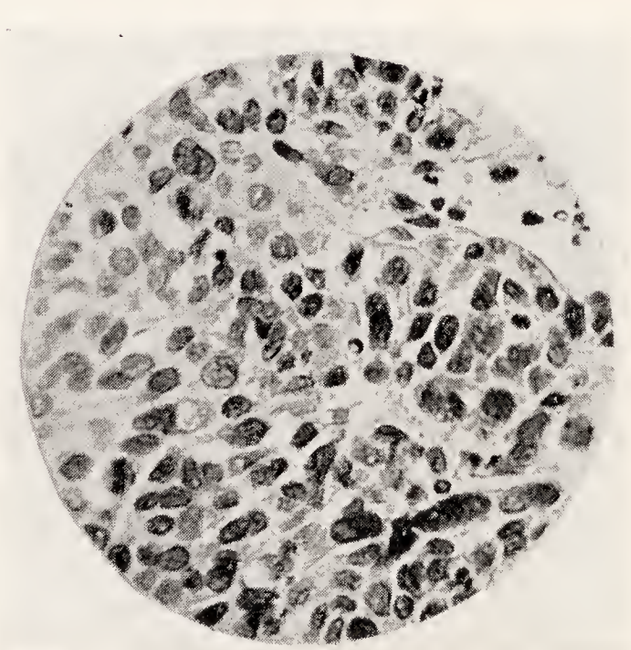

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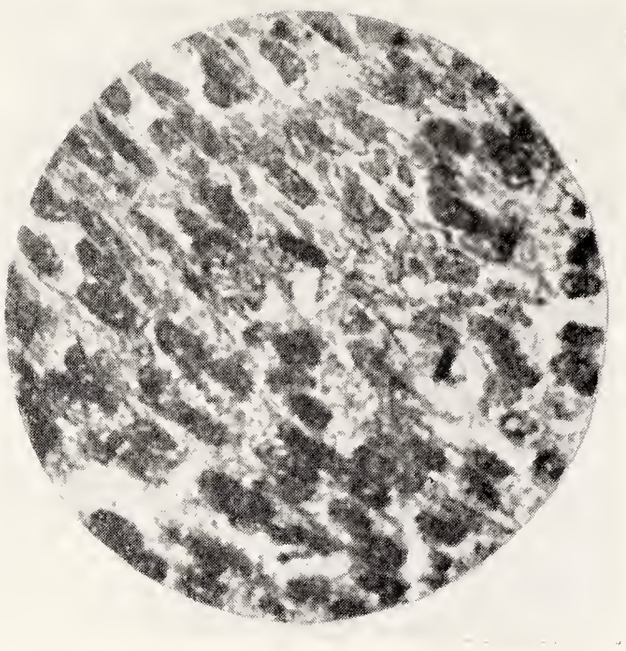

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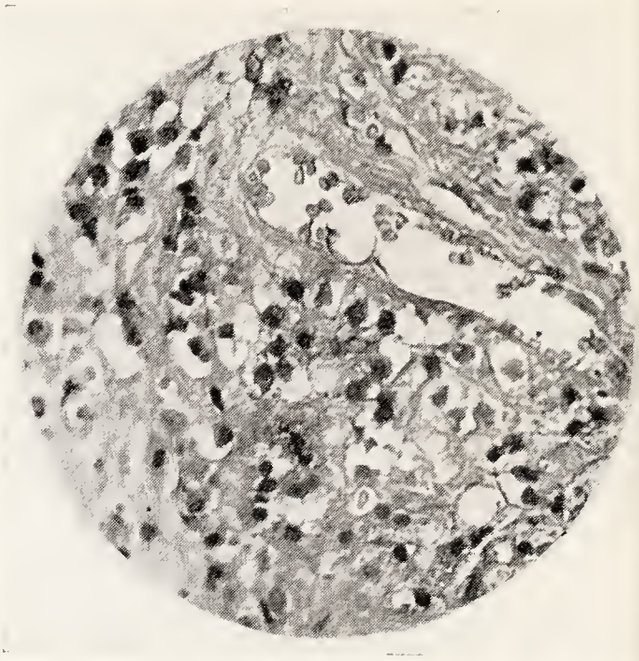

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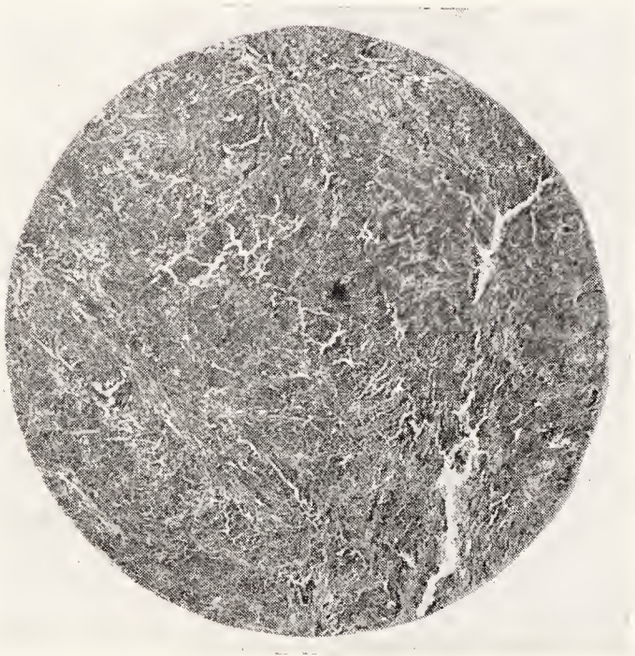

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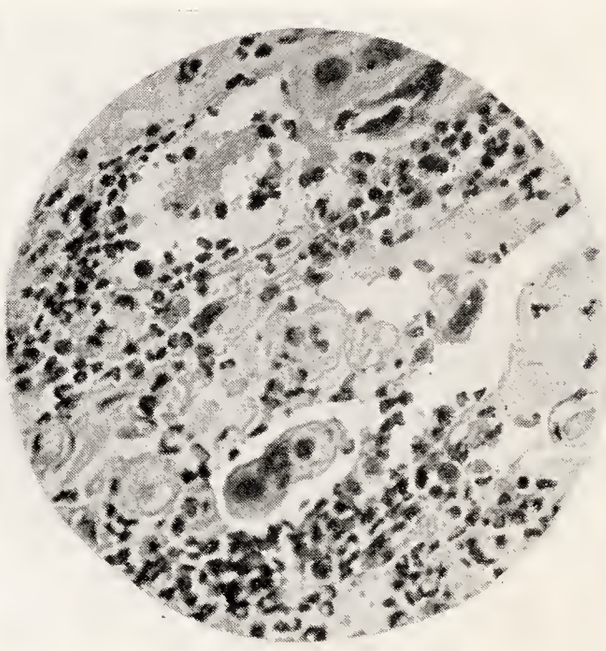

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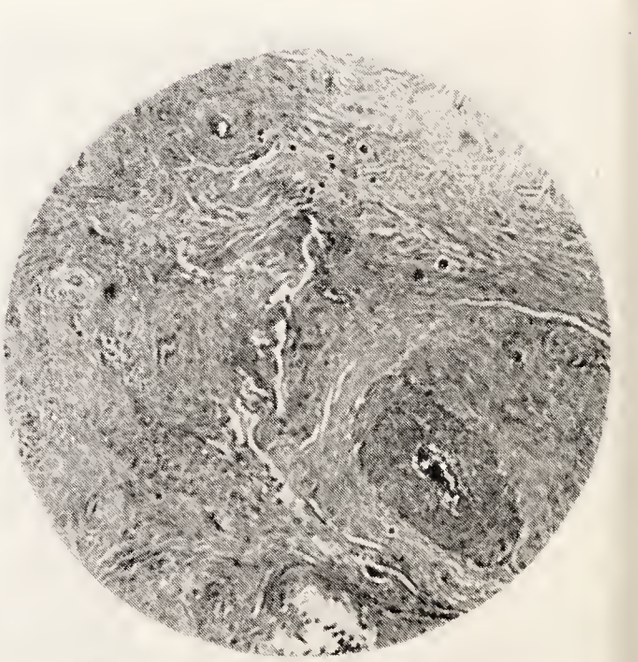

L

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cells are seen which are so atypical that malignancy could not be diagnosed from this section. Many mirror-images are seen, and many more spaces void of nucleus and cytoplasm.

I. *Low Power Section* of cancer of cervix; the field is a solid mass of malignant cells.

J. *High Power of Same Section*, showing the large malignant cells and round-celled infiltration.

K. *and* L.—The same tumour after three exposures to radium six weeks after the first. The malignant tissue is broken up into islets and surrounded by fibrous tissues.

M. *and* N.—The last section under higher power shows the great development of fibrous tissue, with the individual carcinoma cells undergoing degeneration.

Does Weak Radiation Stimulate Tumour Growth?

Wood and Prime[9] observed that certain tumour cells grew more rapidly after radiation *in vivo*, but these experiments were inconclusive, inasmuch as the exposure to radium was a short one, and the experiments too few to justify such deductions. Clinical experiments have been undertaken by Hastings, MacCormac, and Woodman.[10] They exposed secondary skin nodules to radiations from pitch-blende with a potency of one-millionth that of an equal quantity of radium. The skin nodules showed no clinical differences after some months from nodules not irradiated.

Histologically the radiated nodule gave evidence of the effect of even this small dose, being precisely similar but less marked than the effects of adequate dosage. Clinically, the writer has not met a case in which he even suspected a stimulation of the tumour cells, and a very extensive literature does not provide

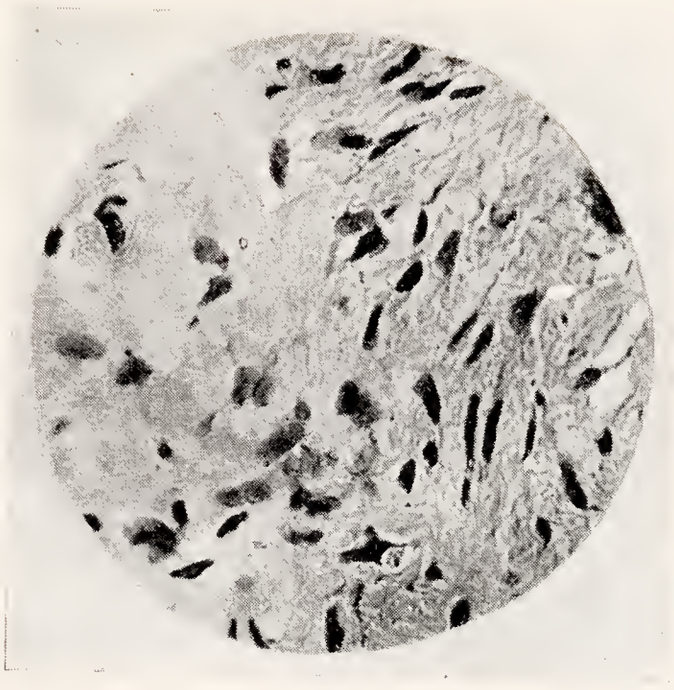
material for considering it as one of the limitations of radium therapy.

Problem of Immunity.

Contamin showed that if tumour cells were first irradiated and then inoculated into mice, the mice exhibited some degree of immunity, and noted that excessive irradiation destroyed the immunity-conferring power of the inoculated cells. Wedd, Morson, and Russ confirmed these observations with the Twort tumour, and carried matters a step further. They noted that if normal tumour cells and radiated tumour cells were inoculated at the same time no immunity was produced. These experiments are too few in number to justify the obvious conclusion, but work along these lines has been carried on by Russ with some success.

It has been claimed that the successful irradiation of a primary growth has been followed by the disappearance of the secondary nodules, and it has been suggested that substances have been set free from the irradiated tumour which act upon the secondary nodules. Such experiments must be viewed with considerable doubt, for surgeons are familiar with the disappearance of secondary papillomata of the peritoneum when the offending ovary is removed, and with the occasional disappearance of secondary nodules of chorion-epithelioma following hysterectomy.

Murphy and Norton[11] in a series of experiments showed that the resistance of an animal to tumour growth is dependent on the activities of leucocytes, and that in animals immune to tumour growth a leucocytic crisis occurs in the blood when tumour cells are inoculated—a crisis which is absent in non-resistant



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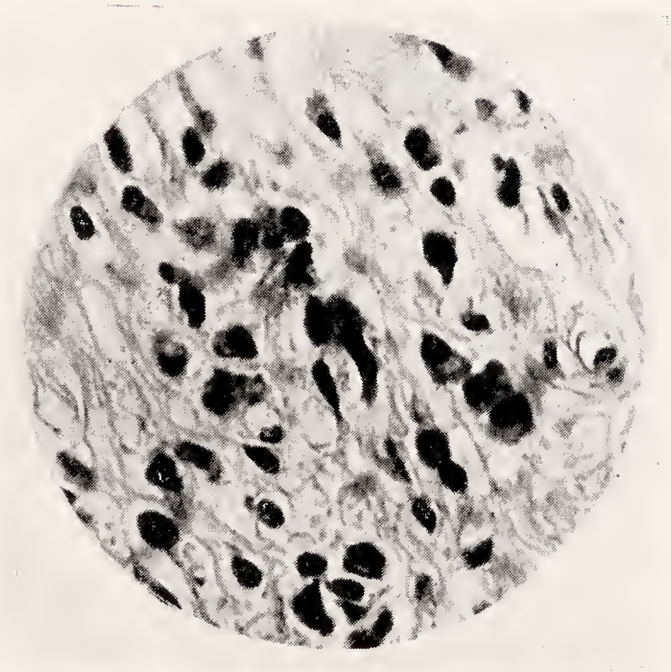

N

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animals. This observation is of great interest clinically where it is known that an ulcerating cancer depresses the leucocytic index, a depression which is accentuated when the patient is irradiated.

The investigators named carried out a further series of experiments. A spontaneous tumour was excised from a mouse, then a stimulating dose of X-rays was given, and a graft of the excised tumour was freshly implanted in the groin. Of fifty-two mice so treated twenty-six were found resistant to the graft, and in the other twenty-six growth was greatly retarded. These results emphasise that the problem is not solely the tumour, but that a greater factor is the resistance of the individual.

Reaction to Radium.

(A) Constitutional Reaction.—Some patients are peculiarly sensitive to radiation, a mild toxæmia being exhibited even in cases where there is no absorption of tumour products. These patients experience nausea and vomiting, which sometimes ceases with the removal of the radium, but in some cases these conditions may persist for some days or even weeks. The majority of patients, however, are quite tolerant of radiation and experience no disagreeable phenomena. With the rapid absorption of an irradiated tumour, symptoms of an acute toxæmia occasionally supervene —nausea, vomiting, anorexia, with a temperature of 101–2°, and a somewhat prolonged mental reaction. The toxæmia usually subsides, but in one case under the writer's observation it persisted to the end.

(B) Local Reaction.—Wickham and Degrais pointed out that radium rays appeared to affect tissues in two different ways:

(*a*) *Inflammatory reaction* with its four degrees, erythema, vesicles, ulcers, etc.

(*b*) *Selective reaction* in which some skin tumours disappeared without any sign of inflammation. Keloids, angiomata, and certain epitheliomata just faded away without visible reaction. It is inferred that the rays deliberately act upon these abnormal cells without affecting the normal tissue cells, and this selective action enables the clinician to radiate tumour cells, without destroying normal tissue, by the employment of suitable dosage.

General Considerations in the Radiation of a Tumour.

It is established that some tumours are more easily destroyed by radiation than others—*e.g.*, a round-celled sarcoma is much more readily influenced than a carcinoma. But this response is not uniform, as other factors have to be considered—*e.g.*, the resistance of the patient, site and size of the tumour, the state of the tumour (whether ulcerated and infected). The size of a tumour is of great importance, as it influences the dosage and technique of the irradiation, which requires that the tumour should be evenly irradiated. The site of a tumour is of considerable importance—*e.g.*, rodent ulcer of the skin is easily cured, whereas rodent ulcer involving cartilage or bone is but rarely influenced. A virulently infected malignant ulcer responds in a very uncertain way—*e.g.*, cancer of the cervix when badly infected may not respond at all, or a massive necrosis may occur, opening up the uterine arteries with severe hæmorrhage. Again, it is found that the primitive embryonic tissues, epiblast, mesoblast, hypoblast, and their derivatives respond differently. Lazarus Barlow found, as a result of his classical experi-

ment upon the epithelium of the bowel and squamous epithelium of the rat's tail, that less damage was done to normal columnar epithelium when the time of exposure was short and the quantity of radium large, than when the quantity was small and time long. In the case of squamous epithelium he observed the reverse effects, and from these data Hayward Pinch[12] has evolved a rough working formula for dosage. $D = Q \times T$.

D = dosage expressed in milligram hours.

Q = amount of radium bromide in milligrams.

T = length of exposure in hours.

Epiblastic tumours appear to be influenced more when Q is relatively low and T high.

Hypoblastic tumours when Q is relatively high and T low.

Mesoblastic tumours occupy an intermediate position.

It must be emphasised that this is not a rigid formula, and that laboratory experience will require sharp modification when clinical cases are approached.

The methods of irradiation have advanced considerably from the early days, and with a greater measure of success since the introduction of radium needles. At first it was the custom to attack the growth frontally with a mass of radium presented at the clinical bulk of the tumour. To-day the principle of crossfire, with special appreciation of the growing edge of the tumour, so that the growth is attacked on all sides at one and the same time, has materially increased the success of radiation in cancer. The general opinion of surgeons remains much the same—viz., where a tumour is operable, operate; nevertheless, the trend of opinion appears to be moving in the direction of narrowing the limits for a radical operation and enlarging the

field for radium. This move is notable in America, Spain, France, Denmark, and Germany, where radium has been longer in use and more readily obtainable; but even in England there are indications that surgeons experienced with radium are becoming anxious to treat early cases. This is more especially marked in cancer of the cervix, where an increasing number of surgeons have abandoned the extended operation, for all cases other than those where the growth is strictly limited to the cervix, in favour of combined treatment by radium and X-rays. It will suffice to enumerate the names of Kelly and Janeway in America, Bumm, Doderlein, Koernig, and Recassens in Europe, as surgeons who largely rely upon radium for treatment in this form of cancer, and who claim from their cases that radium is not inferior to operation for early cases, and greatly superior in borderline and advanced cases. Taussig[13] collected the results of 1,114 cases of cancer of the cervix treated solely by radium from a dozen different clinics, and found that 20 per cent. of all cases and 30 per cent. of early cases remained free from recurrence for five years and over—figures which compare very favourably with the best operative statistics.

Hayward Pinch (London) and Burrows of Manchester, who only treat inoperable cases referred to them by surgeons, give a favourable account of the treatment, the former having cases remaining well over a period of six, seven, and eight years. Burrows, at the annual meeting of the British Medical Association in 1921, quoted his experience of the treatment of hopelessly advanced cases, and stated that 6 per cent. remained well four and a half years, and 12 per cent. for three to four years after treatment. From these

reports there is overwhelming evidence that cancer of the cervix is curable by radium, and the question arises why fuller results are not obtained. Is it because the method, dosage, and technique is not perfect, or is it that too much is attempted—*i.e.*, treatment limited to late cases? Is it a problem in immunity and increasing the resistance? The immunity experiments in mouse carcinoma are very suggestive. The answer is not for the moment available, but Russ and his co-workers are pushing hard along the path of immunity, and not without results.

Rodent Ulcer.—In the treatment of this disease, radium furnishes its most striking successes, thereby establishing its value to clinical medicine. The results have given it a pre-eminent place in the treatment of this type of growth, and it is regarded as the method of choice with certain limitations. Hayward Pinch reports numerous cases healed after one exposure, who have remained free from six to eight years. The limitations are found in cases :

(*a*) With extensive ulcers and considerable loss of tissue.

(*b*) With ulcers which involve bone, cartilage, or mucous membrane, in which cure is rarely attained ; but palliation, by means of the gamma ray, which arrests the growth and relieves the pain, is a welcome help to the sufferer. The radiation must be carefully studied with reference to the type of growth, and to former treatment by X-rays or carbon dioxide snow, etc., and in all cases it is necessary to carry the treatment well beyond the clinical edge of the tumour, for when recurrence takes place it is inevitably at the extreme edge of the scar.

Ulcers of the hypertrophic type are particularly

favourable, and should be exposed to the destructive influence of the beta rays for a variable time, depending upon the size of the lesion and the amount of exuberant growth. Healing takes place slowly, but the scar is soft and supple.

In the excavating type greater caution is necessary in the dosage, as healing is slow and often imperfect; and with an excessive dose a painful traumatic ulcer may supervene. Moreover, these growths tend to recur, and therefore it is essential that the radiation should be carried well beyond the margin.

Sarcomata. — Different types of sarcoma show marked differences in reaction to radium, and unfortunately the proneness to metastases too frequently renders the successful treatment of the primary growth nugatory. Lymphosarcomata are particularly sensitive to the gamma ray, and the dissolution of a large tumour is unequalled by any other form of radiation. The diminution in size from day to day is a striking feature, and eventually the tumour may entirely disappear. Cases are reported as remaining free for considerable periods of time, but metastases occur sooner or later, and in inaccessible places like the mediastinum. Burnham[14] has recorded a group of eight cases of mediastinal tumour treated by radium with considerable success.

Periosteal sarcomata respond well to radium, and appear to have their malignant character destroyed, the patients remaining clinically cured for years.

Spindle-celled sarcomata offer the best prognosis, although they do not respond so rapidly as the round-celled form, yet they rarely recur.

Melanotic sarcomata are frequently benefited temporarily, but metastases generally occur in a short time.

In this form of sarcoma the beta ray may be used for its destructive effect.

The treatment of sarcomata is by means of the gamma ray, and all parts of the tumour should be equally irradiated, which requires a large amount of radium. The ideal method is to bury radium in the tumour, so distributing it as to irradiate the whole tumour; but there are two considerable risks to be met: (*a*) In a vascular tumour the hæmorrhage may be difficult to control; (*b*) incision opens the door to infection. A second method is to bury radium peripherally and irradiate the tumour through the skin centrally, but large quantities of radium are required for this. It is following the absorption of one of the large sarcomata that symptoms of toxæmia are encountered, which may be slight or severe.

Carcinoma.—The writer has treated a considerable number of cases of carcinoma uteri, cervix, vulva, vagina, and epitheliomata of the genital skin, and the following observations are in great part a report upon this experience.

Carcinoma of Cervix.—In general it may be noted that the younger the patient the worse the outlook, and that the best results are obtained from patients at or following the menopause. Again, in the type of carcinoma which is described as endocervical the prognosis is grave, for they are rarely diagnosed in the early stage, and rapidly spread out into the parametria. The squamous epithelioma presents macroscopically two forms:

(*a*) The fungating upstanding type, where the tissues appear to resist the encroachment of the growth; this form responds best to radium treatment, and the clinical successes noted belong to this type.

(*b*) The plunging type of growth, where the tumour burrows into the cellular tissues of the pelvis, where all the uterine ligaments appear to be thickened, and where the surface of the growth is represented by an ulcer with little or no cervix remaining. This type does badly, and is frequently too advanced when first seen to attempt even palliation of the symptoms.

In the treatment of inoperable cases of carcinoma of the cervix, 5 to 10 per cent. are found too far advanced even for palliative treatment—viz., patients with fistulæ, paralysis of a limb, pressure symptoms, or obvious secondary deposits in the abdomen. In estimating the proximal results of the treatment, experience teaches extreme caution in using the word "cure," for any remaining indurated tissue which may be regarded as fibrous tissue, too often contains a potential neoplasm, the growth of which may be delayed for many months.

All the cases treated (fifty in number) were too advanced for operation, with the exception of three, which were comparatively early cases. These three cases were operable so far as the growth was concerned, but owing to the patient's physical condition were given over to treatment by radium. An account of these three cases is worth noting.

Case I.—Miss A., æt. fifty-five, menopause six years ago, had noted irregular hæmorrhage for six months.

Per Vaginam.—The cervix and os, nulliparous in form, look normal, with the exception of a drop of blood in the mouth of the cervical canal. On passing a sound through the os it enters a considerable cavity, from which débris and blood are removed. The growth was limited to the cervix on the left, but there was some induration in the right vaginal vault. She had two exposures of 100 mgrms. radium sulphate, each of twenty-four hours, with ten days' interval. She was being treated with intramuscular injections of selenium, which had

produced so much pain at the site of injection as to require morphia to alleviate it. The injections were continued by her own doctor after discharge from hospital following the second exposure. Ten days later she developed acute diarrhœa, followed by large erythematous patches scattered over the body with bullæ in the centre. These burst and became acutely inflamed, with a rising temperature. She was removed to the infirmary, where she died a few days later of an acute toxæmia. Unfortunately, the writer only received this account some time after the burial, so no post-mortem was obtained. On the whole there is a suspicion that the selenium had to do with the rapid termination, but certainly there is nothing to point to cancer being the cause.

Case II.—Mrs. B., æt. sixty-nine. Menopause twenty years ago; offensive discharge twelve months, recently blood-stained. The growth ulcerative in type; uterus fixed, with induration of both broad ligaments. Four applications of radium (100 mgrms.) over a period of four months, which have been supplemented by deep X-ray therapy. The patient is well and free from recurrence eighteen months after commencement of treatment; there is no trace of growth, and the cervix is smooth and healthy.

Case III.—Mrs. T., æt. sixty-five. Menopause seventeen years ago. Irregular hæmorrhage for six months. The vagina was senile. Cervix flush with vaginal roof, and looks normal. On dilatation a soft growth was scooped out of a cavity in the cervix. Microscopic section showed a carcinoma. Three exposures of 75 mgrms. placed in the cervical canal at intervals of ten and sixty days. The patient remains well and free from recurrence one and a half years after treatment. While no inferences may be drawn from such a limited number of cases, yet the facts are significant and sufficiently encouraging.

Case No. I. obviously must be left out of the picture, which leaves two cases at any rate cured clinically.

Inoperable Cases (forty-seven in number).—All these cases were too advanced for operation, many of them indeed being within measurable distance of the termination of life; nevertheless, where there was any prospect of relieving pain, hæmorrhage, or offensive

discharge, they were irradiated. From the point of view of palliation it may be truly said that radium is unequalled, hæmorrhage ceases abruptly within a few days of the exposure in the majority of cases, pain (provided it is not due to involvement of the sacral plexus) is completely relieved in a fair percentage of cases, and reduced to negligible proportions in others. The discharge becomes more watery, and is robbed of its offensive penetrating odour, and the patient is enabled to resume her household duties until within measurable distance of the end. Where the base of the bladder or rectum is involved, little relief can be obtained, and then there is a risk of precipitating a fistula which must be avoided.

Case IV.—Mrs. H., æt. forty-six. The extended radical operation was performed in May; she returned in September with a recurrence in the vaginal vault, and complained of constant pain in the back, for which morphia was required nightly. She had a brown offensive discharge, which was lately streaked with blood.

Per Vaginam.—In the vaginal vault are two sinuses two inches long filled with soft growth. A large mass could be felt in the pouch of Douglas, which was better defined from the rectum.

September 7—Ether.—The growth was removed with a spoon, and a tube containing 50 mgrms. radium sulphate was placed in the left sinus, and one containing 25 mgrms. in the right sinus. Radium removed in twenty-four hours.

September 29.—Seen again with a view to further treatment, but a leucopenia down to 3,000, with only an occasional polymorph, was the deciding factor against further treatment at the time. The discharge was then inodorous, and she felt better; and it was noted that the pain had been so relieved that she had been able to sleep without hypnotic of any kind. She was sent to Eastbourne for a month, and a week after her return home died suddenly of acute cardiac failure.

Two points of interest are shown in this case:

(*a*) The necessity of a blood count.

(*b*) The notable relief of symptoms, pain and offensive discharge.

Case V.—Mrs. S., æt. forty-three. Had suffered from severe and irregular hæmorrhage since her confinement fourteen months ago. She was admitted to hospital, being bedridden through hæmorrhage, intractable diarrhœa, and secondary anæmia, and had become a nursing problem owing to the persistent hæmorrhage and uncontrolled action of the bowels. She looked so anæmic and ill that it was problematical whether she could tolerate any interference involving anæsthesia. The physical signs consisted of an extensive ulcer replacing the cervix, with walls of soft growth, uterus fixed, with both parametria and utero-sacral ligaments involved, and a large mass in the pouch of Douglas.

Per rectum there was a large tumour pressing upon the anterior wall, over which the mucous membrane was movable. Blood count:

Red blood corpuscles = 2,100,000.

Leucocytes = 10,625, approximately normal in differential count.

Blood plates numerous. A few normoblasts present and slight poikilocytosis.

May 5—Ether Anæsthesia.—A piece of growth was removed for microscopic section (squamous carcinoma). The soft growth was removed by curetting, the cavity painted with 10 per cent. $CuSO_4$ solution, and 100 mgrms. radium sulphate in three tubes (50, 25, 25), screened by 0·5 mm. Ag and 1 mm. brass, covered with rubber tubing 3 mm. thick, was placed in the ulcerous cavity. Radium removed twenty-four hours later, and the patient was nursed on an open balcony with free diet and stimulants. Colloidal copper was given intramuscularly—3 c.c. into the buttock alternately with 5 c.c. into a vein—on the first, fourth, seventh, tenth, and fourteenth days, with fourteen days' intermission before the next series. In addition, half a grain cacodylate of soda was given on alternate days for three weeks.

Fourteen Days Later.—The radium exposure was repeated under anæsthesia, but the ulcer had so contracted down as to only take one of the tubes, the other two having to be stitched to the vaginal vault. Following the first exposure there had

been a complete cessation of hæmorrhage after the first three days. The mass in the pouch of Douglas had contracted to such an extent that it no longer indented the wall of the rectum. The intractable diarrhœa was so modified as to enable the patient to indicate in time the necessity for a bed-pan, and later it entirely disappeared. In two months she was getting about and assisting in the ward. *By September* 1 she was sent to out-patients with a note to say that the lesion was healed and could she return home? On vaginal examination the ulcer was healed, and the vaginal vault showed a smooth and supple scar at the apex of a contracted canal. The mass in Douglas' pouch was present, but much smaller, and could be well defined from the rectum, though not producing pressure. She looked well and felt well, and was anxious to return home. A brief stay in a convalescent home convinced her that she was strong enough to look after her home with three children. She remained well until the following January, when diarrhœa set in again, and she died of exhaustion after an illness of three weeks.

This case demonstrates the dramatic control of hæmorrhage by exposure to radium; it further shows to what an extent the disease is palliated, symptoms relieved, and the patient restored to an economic life until near the end.

A virulent infection of a malignant ulcer of the cervix is a danger if exposed to radium without a preliminary course of cleansing. In these cases massive necrosis may occur, opening up new tissues, including the uterine arteries, giving rise to severe secondary hæmorrhage, necessitating ligature of the internal iliacs before it is controlled.

Case VI.—Mrs. P., æt. thirty-eight years eleven months. Miscarriage in November, 1920, for which she was curetted. A month later irregular hæmorrhage set in, which has steadily increased until she came for advice, October, 1921.

Per Vaginam.—Vaginal cervix has disappeared, and is replaced by an extensive ulcer which involves the vaginal roof all round. The wall of the ulcer is composed of soft, friable tissue, which comes away freely when touched, and has a

sickly odour. The floor of the pelvis is a mass of growth, and the uterus is fixed. She is a frail woman, with pronounced anæmia. The blood count shows a secondary anæmia, with a slight diminution in white cells, but the differential count approximately normal.

October 18—*Ether Anæsthesia.*—A piece of tissue removed for microscopic section (squamous carcinoma), and the soft growth removed with the curette. A hundred mgrms. radium sulphate was placed in the ulcerous cavity and held in place by a catgut stitch.

October 24.—The ulcer remained in an unusually septic condition, presenting a grey sodden surface with considerable œdema, and the unabated odorous discharge.

October 30.—A quantity of necrotic tissue came away in an arterial gush of blood; the bleeding was severe and persistent, and was controlled by plugging the vagina with gauze. The bleeding continued for the next two days, but in gushes at intervals, and it was decided to repeat the radium exposure the next day.

November 2.—Radium again implanted in the ragged septic ulcer and removed in twenty-four hours.

November 3.—Further arterial hæmorrhage, which required plugging, and an intravenous saline to restore the circulation. The writer was sent for, and it was clear that she could not tolerate further loss. Under gas, oxygen, and ether the abdomen was opened, and both internal iliacs ligatured. She recovered, and was later discharged from the hospital, but died a few weeks afterwards.

This patient had not received the usual preliminary rest in bed and cleansing douches, owing to her precarious condition when admitted. The hæmorrhage was secondary as a result of the infection of the arterial wall, and the radium precipitated the hæmorrhage by producing a massive necrosis in highly-infected tissue.

Excessive doses may produce a radium burn, which may be followed by severe arterial hæmorrhage, requiring ligature of the iliacs (internal), or a urinary or rectal fistula.

Case VII.—Miss C., æt. twenty-five years. A virgin; came under observation November, 1921, with definite symp-

toms of eleven months' duration, but indefinite symptoms of nearly two years. The signal symptoms were floodings and pain.

November 18—*Ether.*—The cervix is represented by a mass of new growth, involving the vaginal wall all round. Uterus fixed, and induration of the parametria and both utero-sacral ligaments. A piece of tissue removed for microscopic section (columnar carcinoma), and the growth removed by curette. Three tubes of radium inserted side by side in the ulcerous cavity; removed in twenty-four hours.

November 25.—Radium repeated, but the cavity would only admit one tube, owing to contraction, the other two being stitched to the vaginal vault. Radium removed in twenty-four hours.

December 19.—Returned from Brighton; feels well, looks well, and has gained seven pounds in weight; has completely lost the pain, has had no hæmorrhage, and the discharge is better.

Ether.—Cervix is firm and healthy, and the ulcer is healed. Indurations in parametria remains as before. The cervix was dilated and a 50 mgrm. radium tube placed in it; 2×25 mgrms. were stitched to the vaginal vault. Radium removed twenty-four hours later.

Three weeks afterwards she was admitted as an emergency for severe flooding, following two lesser ones, which came on while at her work. It was doubtful whether she could stand any further loss, and it was decided to ligature the internal iliacs, which was done at once, and it was noted that the glands along the iliac vessels were infected with growth.

Per Vaginam.—The ulcer remains healed except at one spot, where a clot plugs an irregular opening. She recovered and had no more hæmorrhage, but died some nine months later with an extensive growth in the pelvis, producing pressure symptoms on the rectum.

This case is of considerable interest, because the late arterial hæmorrhage is believed to have been due to a radium burn, owing to excessive dosage. The cervix was healthy, the surrounding tissues firm and non-infected, and the ulcer covered with epithelium until after the third exposure to radium, when the hæmorrhage set in in under three weeks. The ulcer had broken down in one spot through which the hæmorrhage was taking place.

Further, it points to the futility of radium, except for the primary growth, in metastatic deposits in the pelvic glands, for they are situate beyond the effective radius of radium.

A second case of a similar nature has occurred in the series of cases under review.

Chronic pelvic inflammation results in a curious condition, where the pelvis becomes filled with a mass composed of omentum, bowel, tubes, ovaries, and uterus all bound together by large firm masses of fibrous tissue.

Case VIII.—Mrs. C., æt. forty-nine, M. 1, complains of an offensive discharge and bleeding on coitus for six months, with severe bearing-down pains.

Per Vaginam.—The anterior lip of the cervix is replaced by a mushroom growth one and a quarter inches in diameter, which breaks down easily and bleeds profusely. The growth involves the vaginal wall, and extends outwards into the base of the broad ligament. The posterior lip looks normal. The uterus is fixed, and both Fallopian tubes are thickened.

September 6—*Ether.*—A piece of growth removed for microscopic section (squamous epithelioma), and the remainder removed with scissors. Cervical canal was dilated and a tube containing 50 mgrms. inserted, two tubes, 25 mgrms. each, being stitched across the anterior lip. Radium removed in twenty-four hours.

September 19.—Bearing-down pain had ceased; she had had no more hæmorrhage, and the offensive odour of the discharge had disappeared. The anterior lip presented the appearance of a healthy healing ulcer.

October 4.—Radium applied as before; piece of tissue removed from anterior lip for microscopic section. Ten c.c. colloidal selenium given intravenously. Selenium repeated on seventh, tenth, and thirteenth day. On the last occasion some of the selenium escaped into the subcutaneous tissues, and produced such an amount of pain that she refused further treatment.

Four months later she was admitted to a general hospital for an abdominal tumour arising out of the pelvis, and which was regarded as an ovarian tumour. The notes read: "On pelvic

examination there was some hard scar tissue in the left fornix, and the cervix was shrivelled up and described as atrophic cervix ; there was no bleeding or ulceration."

"*At Operation.*—The tumour was found to be a mass of dense adhesions, involving omentum, sigmoid flexure, tubes, and ovaries, and after great difficulty the left tube and ovary was removed. The ovary was a bag of pus, and both tubes contained pus ; but the chief thing was the dense sclerosis."

October 5, 1922.—She again reported in out-patients, and was found to have an extensive recurrence of the growth, involving both the bladder and the rectum. The points of interest are :

(1) The local lesion was so thoroughly healed that the surgeon in the general hospital questioned the original diagnosis of carcinoma of the cervix, and deprecated further treatment.

(2) Where chronic pelvic inflammation exists, exposure to radium carries a considerable risk of lighting up the infection and producing abscesses and large inflammatory tumours, and the difficulty of operating upon such cases is considerable.

A serious limitation of radium treatment is the fact that short of opening the abdomen, it is not possible to say whether the glands are involved, and if they are, the irradiation of the primary growth is merely a palliative treatment, for the glands are too remote to be treated from the vagina. The glands are found to be affected with growth in 30 per cent. of the cases that come to operation, and various attempts to deal with them by radium have resulted in ingenious operations for bringing the radium to the infected area without opening the abdomen (Donaldson[15]). Such operations only appear to add a new terror to the disease. The writer has frankly opened the abdomen, implanted the radium in the secondary growth, fixed in a long piece of drainage tube, removing the tube and radium in twenty-four hours. The result was satisfactory in so far as the tumour mass diminished considerably in

size; but the inherent weakness lies in the necessity for opening the abdomen three or four times in order to complete the exposures. The most promising method of dealing with pelvic metastatic deposits is that advocated by Recassens.[16] He places the radium in the cervical canal in the middle of the cancerous growth and uses hard X-rays for the pelvic glands and cellular tissues. He has been employing this method for many years with 25 per cent. five-year cures, but anticipates better results with the new machine capable of standing up to 200,000 volts.

Case IX.—Mrs. S., æt. forty-five, M. 11. Complained of pain in front and back passages for two months, with frequency of micturition, some discharge, and slight hæmorrhage on coitus and douching. Came under observation in May, fourteen months after the extended radical operation for carcinoma of the cervix.

Per Vaginam.—In the roof of the vagina is a mass of new growth with an ulcerated surface. The growth extends outwards in the floor of the pelvis on both sides, and involves the bladder in front.

June 2—*Ether.*—The growth was removed by gentle curettage, and 100 mgrms. radium in three tubes, screened with 2 mm. lead, were placed in the cavity. Great care was taken in packing away the bladder and rectum by means of a long strip of gauze introduced into the vagina, and, as usual, a self-retaining catheter was left in the bladder. The radium was removed in twenty-four hours.

Note on June 21.—"Since application of radium there has been complete cessation of pain and hæmorrhage; the discharge remains thin and odourless. *Per Vaginam.*—The ulcer is smaller, clean and smooth walled; the surrounding infiltration is not so extensive. General improvement."

Ether.—Radium was again applied as before and removed in twenty-four hours.

July 18.—Patient complains of vesical tenesmus and some pain in the back.

Per Vaginam.—The ulcer is contracted down so as only to

admit the point of a probe, and slight oozing takes place on probing. General condition is well maintained.

August 30.—Patient has complained of pain and frequency of micturition for three weeks, but no incontinence.

Ether.—The ulcer is small and healthy, and covered with a superficial grey slough. On washing out the bladder the saline comes trickling out through the ulcer.

September 19.—Incontinence of urine with irritation of the vulva.

Where the growth involves the base of the bladder, there is always a grave risk of precipitating or producing a vesico-vaginal fistula. Whether in this case the radium had anything to do with the production of the fistula, or even of hastening the advent, is open to doubt. Nevertheless, the appearance of that grey membrane-like slough is strongly reminiscent of the late radium ulcers, and made one suspect that it was not entirely blameless.

The remainder were inoperable cases, forty-seven in number.

Four are clinically free of disease over a period of six to twelve months, which means that they are free from all symptoms, and that they are free from growth so far as can be determined by physical examination; time alone will tell how near they approach to the artificial five-year cure.

Eight remained unrelieved, mainly because they were too far advanced, when treated, for any great change to be expected.

Three were lost to observation, and three abandoned treatment.

The remaining twenty-nine, many of whom are since dead, received marked benefits from cessation of hæmorrhage, relief of pain, and modified discharge.

Carcinoma of the Fundus.—This condition is much rarer than carcinoma of the cervix, and operative

treatment gives such excellent results that all cases should be submitted to hysterectomy where possible. The writer has treated three cases of this disease, all passed to him as inoperable, the diagnosis in each case being based upon clinical and microscopic grounds. One had undergone abdominal section, with a view to panhysterectomy, but the growth had involved the peritoneal surface, with massive adhesions, and the operation was abandoned. She remains well after one and a half years of treatment.

Case X.—Mrs. B., æt. fifty-one, M. 4. Came under observation May 5, 1921, with a microscopic diagnosis of cancer of the fundus uteri. Abdominal section had been performed with a view to panhysterectomy, but the growth was found to have extended to the Fallopian tubes, and the abdomen was closed, the growth being regarded as inoperable.

Ether.—One hundred mgrms. radium sulphate, screened with 0·5 mm. silver and 1 mm. brass, was introduced into the uterus, which was considerably enlarged. Radium removed in twenty-four hours. The pain and hæmorrhage ceased from the time of exposure; she recovered her usual health and remained well until November, 1922, when she reported a blood-stained discharge for ten days.

December 6, 1922—*Ether.*—The cervix was œdematous and showed a papillary erosion, the uterus a little enlarged, but freely mobile. The cervical canal was dilated and the endometrium curetted, but found to be smooth and firm, no tissue coming away. Radium introduced as before, and the cervix was painted with iodised phenol. The blood-stained discharge has ceased, and there is no doubt that it emanated from the cervix, and not from the body of the uterus, the latter being free from disease.

One of the others remains well eleven months after treatment, and the third one seven months after treatment.

In all cases the cervical canal is dilated, and 100 mgrms., screened by 1 mm. of silver, is passed

into the uterine cavity, which is repeated two or three times as necessary.

Carcinoma of the vagina is a rare disease, and the writer has treated four such cases. The treatment appeared to delay the growth of the tumour, but in none of them did the growth disappear, and indeed steadily progressed.

Squamous epithelioma, arising in the perineum at the junction of the fourchette with the perineum, was not influenced in any way by exposure to radium.

Adjuncts to Radium.

There are certain cases of cancer which appear to resist radiation after one or two exposures, and it was determined to try the effects of collosol selenium based on papers by Wassermann and Keyser,[17] Watson Williams,[18] and Hayward Pinch.[19] Collosol selenium was given in twelve cases, some by intramuscular injection and some by intravenous injection. No detectable change occurred in either the tumour or in the general condition of the patient. All the patients complained of intense pain at the site of injection, which lasted from a few hours to three days, and in at least one case required morphia to alleviate it. There was some complaint of headache and malaise which quickly passed. In Case I., cited above, there was reason to suppose that the intramuscular (in her case) injection of selenium was associated with an acute toxæmia; hence the use of selenium was abandoned.

Collosol Copper.—Recassens had long been advocating the use of colloidal copper in conjunction with radium, merely as a result of casting about amongst the metals for help in his fight against cancer, when Powell White[20] published a paper upon the results of

his investigation upon the distribution of copper in the vital tissues. He found that—

(*a*) Copper was universally present in the tissues of animals and plants.

(*b*) Copper was present to a greater extent in degenerating tumours than in non-degenerating tumours, and suggested the possibility of the degeneration being due to the catalytic action of the copper.

It was then determined to try a series of cases by injection of collosol copper. Twelve cases were treated, one of whom showed slight toxæmic symptoms after the third injection and in whom it was consequently discontinued. There was a certain amount of pain at the site of injection in most of the cases; otherwise there was no untoward symptom. It is difficult to assess the effect scientifically, but the impression gained is in favour of continuation. A tumour which seemed recalcitrant to further exposures of radium showed response when copper was given as well, the ulcer showing a tendency to contract down more; the discharge was not so often complained of, and the moral tone appeared to be improved. These are, of course, vague impressions, and not evidence from which to draw any inferences; nevertheless, they compel one to continue the use of copper.

The histological changes occurring under radiation have been described above. The macroscopic changes are striking. By the end of ten days when the second exposure is given the ulcer has undergone contraction, the floor is clean and the edges granulating and firm, with epithelium covering the more recently formed tissue. There is no bleeding, no further breaking down of tissue, but a thin free discharge. In

general health the patient has improved, as indicated by the colour, appetite, and *bien-être*. The uterus is more mobile, and some of the induration in the pelvic floor has disappeared, being largely inflammatory in origin; rest and preliminary douching serve to alleviate it.

Technique.

In all cases the growth is lightly curetted to remove necrosing tissue. In all cases the cavity is painted with 10 per cent. $CuSO_4$. In all cases a piece of the growth is removed for microscopic section. In all cases where possible the cervix is dilated to take a tube of 50 mgrms., and in all cases two tubes 25 mgrms. each are fixed by catgut suture to the vaginal vault over the outlying portion of the tumour. In all cases the vagina is tightly packed with gauze moistened with liquid paraffin, the object being to press the bladder away in front and the rectum away behind from the radium. In all cases a self-retaining catheter is left in the bladder for twenty-four hours to ensure its being constantly empty. In all cases the rectum has been thoroughly washed out beforehand to ensure its being empty. In all cases two to three days have been spent in bed, and cleansing douches given before the exposure to radium. In all cases a stitch is passed through the labia majoræ to ensure the gauze plug support remaining *in situ*. In the majority of cases a hypodermic of morphia is given to ensure the patient remaining quiet. *Blood counts* are invariably made. Three exposures are given at ten-day intervals, then six weeks' interval may be followed by further exposures, but the later exposures are entirely by the gamma ray, the earlier exposures

being to beta and gamma rays, depending upon the thickness of the growth and the amount of fungation.

In cases where radium needles or emanation tubes are available, the main radium tube should still be placed in the cervical canal in the middle of the growth, with a radial disposition of the needles or emanation tubes into the outlying parts of the growth, particularly the bases of the broad ligaments. In this way a more intimate general irradiation of the tumour is given.

Prophylactic Radiation.

The policy of irradiating a tumour before operation has been strongly advocated, with the object of influencing the outlying malignant cells in the event of some not being removed at operation. Equally, post-operative radiation has been advocated with the same object.

Pre-operative Radiation.—(*a*) *Radiation three to four weeks* beforehand is followed by such dense fibrosis that the complete operation is rendered very difficult and sometimes impossible. The ureters are buried in sclerosed tissues of such density that it is impossible to free them, and surgeons have had to abandon the operation on that account.[21]

(*b*) *Radiation Two to Three Days before Operation.*—Graves[22] reported a number of cases treated in this way, and amongst them three cases of post-operative peritonitis, one fatal, which he attributed to the preceding irradiation; hence he abandoned this method.

(*c*) *Radiation Nine to Twelve Days before Operation.*—Many surgeons now employ this method, thereby avoiding both the above difficulties, and no disadvantage has been reported.

Post-operative Radiation.—Great caution is necessary in this form of treatment, for the tissues remaining after an extensive operation are benumbed and ill-nourished for some time, and early exposures have resulted in massive necrosis and hæmorrhage. Such radiation should not be undertaken for two to three months after the operation, and in pelvic cases the presence of the bladder in front and the rectum behind must be ever borne in mind lest a fistula result.

What Place does Radium Occupy in the Treatment of Malignant Disease?

Radium has won its spurs in clinical medicine in virtue of its influence upon malignant tumours. In rodent ulcer and certain types of sarcoma it has succeeded in curing beyond a peradventure. There is an abundance of published evidence that in cases of cancer of the uterus the disease had disappeared for over the artificial five-year cure period, which evidence covers early and late cases. The question then arises: "Are we to continue to treat only inoperable cases? Is it not time that a series of early cases were treated by a team of workers, so that a final opinion may be formed?" Burrows has come to the conclusion that with the late material with which he has to deal the limit of success has been reached. The reports from Hayward Pinch and Burrows are sufficiently encouraging to warrant the next step of fighting cancer at an earlier stage with radium. The argument in favour of early appeal to radium is particularly applicable to cancer of the cervix, for the disease is still more or less localised by the time the patient comes under observation, and the operative field is very

limited in comparison with operations upon the breast and alimentary canal.

As a treatment for late cases of cancer there is no comparison with any other treatment known. In 80 to 85 per cent. of cases the symptoms are relieved with the minimum amount of invalidism, and the patient is enabled to pursue her daily round without inconvenience to herself and without being a nuisance to others.

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THE TREATMENT OF SEVERE AND PERSISTENT UTERINE HÆMORRHAGE BY RADIUM, WITH A REPORT UPON FORTY-FIVE CASES.*

Severe and persistent uterine hæmorrhage, at any age, is a source of infinite anxiety to both the patient and doctor, and when the doctor has exhausted the long and too often futile list of drugs, together with prolonged periods of rest in bed, he is constrained to recommend curettage. Many of the less severe cases are relieved by this measure, but in the type of case under consideration the relief, if at all, is only measured by weeks, and the patient is too soon in the *status quo ante;* and it becomes clear that something more radical must be undertaken.

At or near the menopause the above palliative measures may suffice to pilot a patient through a stormy climacteric into the backwaters of post-menstrual life, only too often, however, at the cost of transforming the patient into a semi-invalid, with the late prospect of complete neurasthenia. While this method is possible for the well-to-do patient who can afford to remain in bed, it is not feasible for the wage-earner, or the mother of a family, and other means must be adopted to deal with the condition promptly and finally.

The methods advocated for this condition are: (1) Hysterectomy; (2) X-rays; (3) radium; and the

* A paper read at the Section of Obstetrics and Gynæcology of the Royal Society of Medicine, March, 1923.

analysis of a report upon forty-five cases treated by radium tends to show that it is the treatment of choice when available.

Selection of Cases.

The type of case under consideration is sometimes described as the "bleeding uterus"—a most descriptive term; more commonly it is labelled "chronic metritis," "fibrosis uteri," or "chronic subinvolution." But however debatable the pathology, the one distinctive clinical feature is the excessive and uncontrollable hæmorrhage, with absence of any pelvic lesion to account for it. This series of cases does not include the ordinary causes for hæmorrhage, but only cases which had been dealt with in the usual way and proved refractory to treatment. The criteria by which cases were selected were: (*a*) The persistence of severe hæmorrhage after operative treatment; (*b*) an advanced anæmia, with shortness of breath, headaches, œdema of legs, etc., which had been treated palliatively for some time; (*c*) cases in which the patient had to spend some part of each month in bed.

Excluding the three cases in which an effort was made to modify the period rather than to stop it, there were forty-two cases, the youngest patient being twenty-nine years and the oldest fifty-five years of age.

Three only were unmarried, and of the thirty-nine married four only were nulliparæ.

Number and Types of Operations.

Of the forty-five cases, twenty-six had undergone some form of operation, or combination of operations, including dilatation and curettage, removal of polypi, amputation of cervix, oöphorectomy, or salpingo-

oöphorectomy, and some of the cases had been curetted more than once. The remaining cases had undergone medical treatment for variable periods, or their state was so anæmic as to forbid any further effort at palliation.

Clinical Types.

Four cases were associated with fibroids, two of the interstitial variety, and two small subperitoneal fibroids. The results were equally satisfactory, and no change could subsequently be detected in the subperitoneal tumours. While all the uteri were enlarged, they were broadly divisible into two groups, which might be best described as (*a*) systolic uterus; (*b*) diastolic uterus. The systolic uterus was hard, firm, and regular, commonly straight, and admitted a sound for 3 inches to $3\frac{1}{4}$ inches; it yielded little or no tissue to the curette, and gave the characteristic rasp of fibrosis uteri.

The diastolic uterus was bulky, retroverted, admitted a sound from $3\frac{1}{2}$ inches to 5 inches, and generally yielded a thickened and œdematous tissue. An interesting point about this type of uterus was the fact that some months after irradiation it was indistinguishable from the systolic type.

Technique.

In all cases dilatation of the cervix and an exploratory curettage were performed. In cases in which the cervix and vagina were septic a preliminary cleansing treatment was carried out. In all cases the radium was placed in the uterine cavity, and only the gamma ray was utilised. The vagina was packed with gauze moistened with liquid paraffin, with the twofold object of supporting the radium and of keeping the bladder

and rectum away from the source of energy. A further precaution was adopted to maintain the bladder in a flaccid condition by the introduction of a self-retaining catheter into the viscus. In some cases it was necessary to stitch the vulva in order to support the vaginal plug.

Dosage.

In three cases of patients between the ages of twenty and twenty-six, 50 mgrms. of radium were used for five hours. In the other cases, 100 mgrms. were used for twenty-four hours, the object in the former cases being to influence the menstrual period, in the latter cases to end it altogether.

I am inclined to think that 100 mgrms. is an unnecessarily large quantity for the purpose, for in some later cases 75 mgrms. appear to have the desired effect.

A certain number of patients complained of pain while the radium was *in utero*, but no more than when a stem is left in the cervix, and it disappeared promptly with the removal of the radium. In a few cases post-anæsthetic vomiting was prolonged, and this appeared to be relieved by the withdrawal of the radium. Some of the patients noted a frequency of micturition following irradiation, a condition which was quickly relieved by barley-water, citrate of potash, etc. Beyond the above, no untoward symptoms were noted. In all cases nocturnal douches of salt and water are suggested for a period of six weeks following the radiation.

Classification of Cases.

A.—Aged 20 to 26, three cases.
B.—Aged 29 to 38, ten cases.
C.—Aged 39 to 50, twenty-two cases.
D.—Aged 51 to 55, ten cases.

GROUP A will be considered in detail; a selection of cases of other groups is appended.

CASE I.—Aged 20, married, no children. For one and a half years had been losing fourteen to twenty-one days at a time and was only clear from seven to ten days. September, 1921: Dilatation and curettage, which did not relieve her at all, and she attended out-patient department in October, November, and December, and it was evident that something more would have to be done. January, 1922: 50 mgrms. radium introduced into uterine cavity and left there for five hours. Late in January she had a period of four days. February 28: Another period lasting four days. March and April: A more severe period. May: Admitted to another hospital where an ovary was removed. Since then she has been quite well.

CASE II.—Jewess and single, aged 23. She had been losing daily for seven months and was very anæmic. Had already been in hospital twice for the same condition. (1) The first time for six weeks for observation and palliative treatment. (2) Second time for dilatation and curettage; following this she was better for three months, but then relapsed into the daily loss. She was now thoroughly demoralised, and despite her religion was anxious that hysterectomy should be done. In February, 1921, I dilated the cervix and introduced 50 mgrms. of radium sulphate into the uterus, leaving it there for five hours. She bled steadily for eleven days, during which time the vagina had to be plugged. For the next six months she saw regularly each month for from four to six days; during that time she was in sole charge of a hemiplegic father, and since then she has had no period at all. This, I think, must be attributed to the close confinement and hard work involved rather than to the influence of radium.

CASE III.—Aged 26, married, no children. Since marriage she had had severe periods with pain for four years, which necessitated a couple of days in bed per month. She was anæmic and had been treated with drugs for a considerable time. January, 1921: 50 mgrms. radium sulphate placed *in utero* for five hours. Has been regular every month since, three-day type and without symptoms.

Group B.—Aged 29 to 38. There were ten cases, eight of whom had had some form of operation, and two had been treated palliatively and had become steadily worse. *Aged* 29, *one; aged* 34, *two; aged* 35, *one; aged* 36, *one; aged* 37, *two; aged* 38, *three.*

Group C.—Aged 39 to 50, twenty-two cases, eleven of whom had had some form of operation, and eleven had been treated palliatively, but with advancing anæmia and persistent hæmorrhage. *Aged* 39, *six; aged* 40, *three; aged* 41, *two; aged* 43, *one; aged* 44, *one; aged* 46, *four; aged* 47, *one; aged* 49, *three; aged* 50, *one.*

Group D.—Aged 51 to 55, ten cases, five of whom had had some form of operation and five had been treated palliatively. *Aged* 51, *three; aged* 52, *one; aged* 53, *three; aged* 55, *three.*

Symptoms following the Radium.

(1) No further loss in ten; (2) one period in seventeen; (3) two periods in eleven; (4) three periods in four.

The periods usually consisted of long drawn out "shows" varying from three days to three to four weeks, the actual quantity of blood lost being small. In cases where the exposure had been given immediately preceding a period it usually resulted in a severe loss.

In five cases radium had to be employed a second time; in three of them I have little doubt that the first exposure would have sufficed, but the patients were so thoroughly frightened by two prolonged shows following the first exposure that it was considered advisable to comply with their demands. In only two of these five was an anæsthetic necessary.

Vasomotor Symptoms.

Flushing as an index of vasomotor disturbance is liable to a very considerable margin of error, and consequently is open to legitimate criticism. Many women will omit mention of this symptom in a carefully taken history, and yet, when it is suggested to them, they will admit experiencing the symptom occasionally; where flushing is a real signal symptom it is mentioned spontaneously. The graver vasomotor changes as signified by a profuse perspiration or a generalised fall in blood-pressure, are never omitted in the history, for they produce considerable distress. Consequently I have adopted the plan of listening to their history patiently, and if they do not mention vasomotor symptoms I have carefully refrained from asking them, and in the after-result it was a fair conclusion that such symptoms did not exist.

Group A.—Aged 20 to 26. There were naturally no symptoms.

Group B.—Aged 29 to 38, ten cases. Eight had no symptoms; two complained of flushes. This was the group in which one would have expected to find vasomotor symptoms on the assumption that the ovary was being affected.

Group C.—Aged 39 to 50, twenty-two cases. Nine had no symptoms; four, flushing; three, flushing and sweating; six complained of flushing before treatment, which remained the same afterwards.

Group D.—Aged 51 to 55, ten cases. Six suffered from flushes before treatment and remained much the same; four made no mention before or after.

What is the Cause of Radium Menopause?

Is it due to action upon the uterus, or the ovary, or both? The available evidence points to action upon the uterus solely in the majority of cases, and is based upon (*a*) clinical, (*b*) experimental grounds.

(*a*) Clinical Evidence.—In the younger women aged from twenty-nine to thirty-eight only two out of the ten mentioned flushes, where this symptom should have been pronounced, on the assumption that the ovary was influenced. Again, in the group thirty-nine to fifty the symptom was not unduly increased, and only in three cases was sweating added to flushing. Histological evidence is difficult to obtain, for removal of the uterus following treatment by radium for this condition must be very rare. However, by the courtesy of Dr. Miles Phillips, of Sheffield, I have examined sections from two uteri after exposure to radium, and a section of the ovary from one of the cases. In the uterine sections there was a diminution in the number and size of the glands of the endometrium, and fewer capillaries than normal, but in the ovary there was no change suggestive of irradiation.

(*b*) Experimental Evidence.—The normally placed ovary is 8 cm. away from the uterine cavity, and beyond the effective range of radium, but a prolapsed ovary would be very much nearer and to some extent would account for variable results. The uterus of a cat being bicornuate, the conditions under which radium is used clinically can be reproduced by the implantation of the radium in one horn whilst the contralateral ovary is fixed by a stitch at 8 cm. distance from it. The experiment was performed in this way. A pregnant horn was opened and the fœtus removed; the radium was then implanted and the horn closed by

suture. The ovary of the same side was lightly attached to the wall of the uterus, and the opposite ovary was fixed at a distance of 8 cm. by suture and rubber tube. The radium was removed in twenty-four hours' time. This experiment was repeated, the animals being killed at intervals of twelve, twenty-one, and sixty days. In none of the experiments did the contralateral ovary show any macroscopic or microscopic change. In all the experiments the ovary of the irradiated side shows a profound change, consisting of complete destruction of both large and small follicles. The corpora lutea are broken up, and in the later survivals there are only a few scattered lutein cells recognisable. Vessels are for the most part obliterated, and few remain normal. The uterus on the affected side shows atrophy of the endometrium, a diminution in the number and size of the glands, and a diminution in the number of capillaries. There is no characteristic change in the stroma cells, although they appear to be fewer; but in the later survivals there are no glands, few capillaries, and a great increase in connective tissue with few stroma cells. [See photo-micrographs, Figs. 1-6.]

I then endeavoured to show that the remaining normal ovary was functioning by breeding from a cat which had been exposed in this way, but hitherto that ambition has not been gratified, mainly, I think, because the condition of the animal and its environment tend to depress the sexual instinct.

Contra-Indications.

The only contra-indication is a previous pelvic inflammation, and this is a very real danger, for the pelvis may become filled with an inflammatory tumour rising into the abdomen, the nucleus of which is an

FIG. 1.—Normal endometrium, low power.

FIG. 2.—Endometrium exposed for twenty-four hours, survival for twelve days. The endometrium is reduced in depth, the glands are reduced in number and size, and capillaries are few.

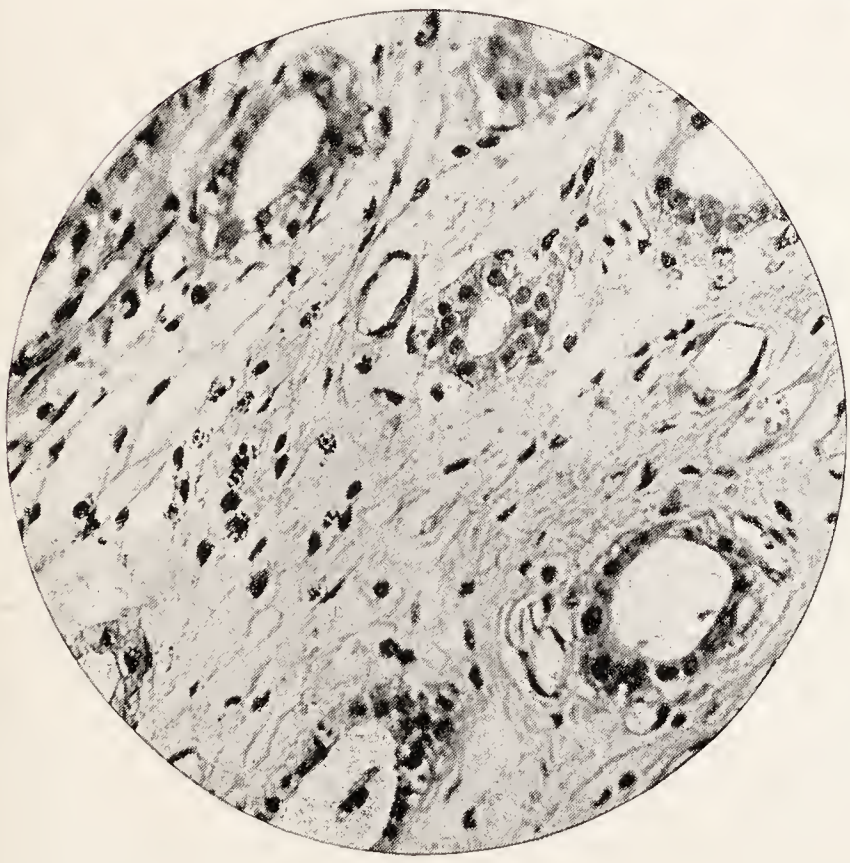

FIG. 3.—The same section under a high power shows some diminution in stroma cells with an increase in connective tissue.

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FIG. 4.—Twenty-four hours' exposure, survival for twenty-one days. Endometrium shows pronounced atrophy, almost complete absence of glands and blood-vessels, and a poorly staining stroma.

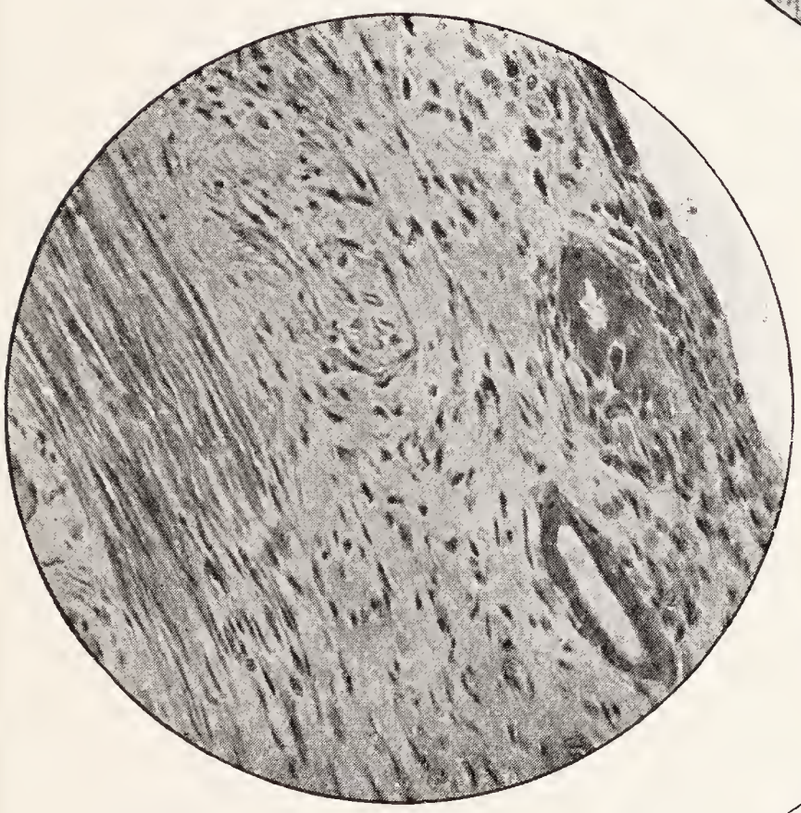

FIG. 5.—The same section under a high power.

FIG. 6.—Endometrium under the same exposure of twenty-four hours, survival sixty days. The atrophy is still more marked, with great increase of connective tissue, and paucity of stroma cells.

abscess deeply seated in the pelvis and nearly impossible to deal with. I have experienced a case of this kind in treating a carcinoma of the cervix, where one had to risk this evil in order to combat the growth.

Relative Advantages of Radium, X-Ray, and Operation.

(*a*) RADIUM is suitable for all, with the exception of cases complicated by inflammatory disease. There is no mortality and no morbidity, and only the minimum amount of time is necessary for the treatment—from three to seven days. There is no prolonged convalescence, stay in hospital or nursing-home. There were no failures in this series. The one drawback is the comparative scarcity of radium.

(*b*) X-RAYS.—The use of X-rays for the treatment of severe uterine hæmorrhage has been fairly successful, but it is accompanied by the following very definite drawbacks: (1) The X-rays are utilised to destroy the ovaries, and their use raises the objection that normal organs are being destroyed in order to influence an abnormal organ, and this is accompanied by a considerable proportion of cases exhibiting severe vasomotor symptoms (38 per cent.: Eden and Provis). (2) The treatment is prolonged, lasting three to four hours on two succeeding days, repeated at intervals of twenty-one days on four to six occasions. (3) There is a danger that the treatment may be used without a diagnostic curettage. (4) Ulceration of the bowel, superficial burns, etc., have been noted. (5) Finally, a certain number of failures have been noted.

(*c*) HYSTERECTOMY, despite its low mortality, is a severe operation, and frequently associated with post-operative results which are difficult to assess—*e.g.*, the

profound depression and loss of morale not infrequently seen. There is a more or less prolonged period of invalidism following any abdominal operation, and a certain percentage of morbidity, as shown by subsequent pain, herniæ, adhesions, and constipation. Nevertheless, the operation is satisfactory, inasmuch as the bleeding is cured beyond a question, and the only criticism is that the subtotal operation leaves a useless cervix, too often a diseased cervix, and less frequently a cervix which may become the seat of a malignant growth, of which I have met one example this year. The drawbacks of this particular treatment to the wage-earner are the length of stay necessary in hospital, the length of the subsequent convalescence, and the problematical complete restoration of health.

Conclusions.

(1) In my opinion radium treatment should be the method of choice in all uncomplicated cases of severe and persistent hæmorrhage due to chronic metritis, inflammatory disease of the tubes and ovaries constituting the sole contra-indication.

(2) The radium menopause is not usually accompanied by any symptoms attributable to action upon the ovaries, and it produces the least disturbance of the patient's economic life.

Epitome of Cases.

Group A.—Three cases, aged 20, 23, 26.

Group B.—Ten cases, aged 29 to 38. Aged 29, one; aged 34, two; aged 35, one; aged 36, one; aged 37, two; aged 38, three.

Group C.—Twenty-two cases, aged 38 to 50. Aged 39, six; aged 40, three; aged 41, two; aged 43, one; aged 44, one; aged 46, four; aged 47, one; aged 49, three; aged 50, one.

Group D.—Ten cases, aged 51 to 55. Aged 51, three; aged 52, one; aged 53, three; aged 55, three.

Multiparæ, thirty-five; nulliparæ, six; single, four.

Periods subsequent to exposure: *Nil*, ten; one period, seventeen; two periods, eleven; three periods, four.

Vasomotor symptoms: twenty-one had no symptoms; nine complained of flushes after treatment; twelve had flushes before and after treatment.

Selection of Cases.

Case XXXVII.—Aged 29, multipara 3. Hæmorrhage for seven to eight days every fourteen days, severe loss. Dilatation and curetting, but the hæmorrhage was worse, not being absent for even one day. Had returned to hospital for a hysterectomy, for which she had been prepared. Radium was suggested and given. The uterus admitted a sound for 3 inches, and the curette gave the hard rasp of fibrosis uteri. Two prolonged periods followed, the loss, however, being comparatively slight. Then a second exposure of radium, followed by a few days' loss, and nothing has been seen since.

Case XXVI.—Aged 37, multipara 3. Had been losing excessively for many months, and showed pronounced anæmia. Admitted to hospital; dilatation and curettage January. Got steadily worse after discharge from hospital, and was uninfluenced by drugs, and then a prolonged loss of eight weeks. June: Radium sulphate, 100 mgrms. for twenty-four hours. After leaving hospital she had a prolonged daily loss for seven to eight weeks; then clear for two months, then a further daily loss for a month, made worse by ergot, etc. Second exposure without anæsthesia, 100 mgrms. radium sulphate. No further loss.

Case XXV.—Aged 50, multipara 4. Daily loss with floodings; large part of her time spent in bed. Secondary anæmia pronounced. Uterus hard, regular and firm, a scanty amount of tissue being removed: 100 mgrms. radium sulphate for twenty-four hours. Two prolonged shows of eight and seventeen days followed, the loss being small. The patient was nervous and insisted upon further treatment. Second exposure given; no further loss occurred.

Case XXXII.—Aged 34, multipara 1. Severe flooding for

one year nine months, and showed pronounced anæmic symptoms. Admitted to hospital, where dilatation and curettage were done. The relief was very temporary, and two months later she was losing as freely as ever. A period of medicinal treatment was fruitless, and she was getting steadily worse. Six months after the former operation radium was placed *in utero*. Three periods followed, the patient again getting gradually worse, and so radium was given a second time, and since that time there has been no further loss.

Case XII.—Aged 51, multipara 6. Severe floodings and constant loss for many months, which drugs did not influence at all; and she spent most of her time in bed. She was not a good subject for a severe operation, and therefore radium was given a trial. After the first exposure there were two prolonged shows, but the loss was comparatively slight. However, the patient was demoralised, and insisted upon further treatment, and, accordingly, a second exposure was given. A recent letter from her doctor informs me that she had had no further loss, and she feels well.

Case XIX.—Aged 49, multipara 2. Catamenia fourteen to seventeen days, every twenty-one to twenty-eight days. Anæmia. Interstitial fibroid. Had been treated by palliatives for some time, and was no better. Radium followed by one show, which lasted twenty-one days. Has seen nothing since.

Case XXXIX.—Aged 39, single. Severe and prolonged periods, treated by palliatives; no relief. Small interstitial fibroid present; 100 mgrms. radium sulphate for twenty-four hours. Two shows subsequently of two and ten days. No further loss.

Case XLII.—Aged 46, multipara 1. Catamenia eight to ten days every twenty-one to twenty-five days, with severe loss. *Per vaginam* two small subperitoneal fibroids, the size of marbles, could be felt, one anteriorly and the other posteriorly. Exposure to radium. One show of three days subsequently, then no further loss. The fibroid in the anterior wall, by reason of its position in relation to the bladder, would have to be removed if it showed any increase in growth. So far, however, it has remained of the same size.

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